



# Edinburgh Medical Journal

January 1947

## BALLANTYNE'S GHOST\*

By R. W. JOHNSTONE

THE period of enforced hibernation of our Society through six years of war and more than a year of its scarcely less strenuous and troubled aftermath has now ended. The time has come for us to bestir ourselves in the Society's interests once more, for even in these years the progress of obstetrics and gynaecology has not been arrested, and there are many topics that we might discuss with interest and edification.

In 1938 you did me the great honour of electing me for the second time to be your President, and I had the unique privilege of occupying this distinguished position during the spring of 1939 when the Society celebrated the hundredth anniversary of its existence. By a happy chance this centenary coincided with the opening of the Simpson Memorial Maternity Pavilion of the Royal Infirmary. By an equally happy pre-arrangement, the Eleventh British Congress of Obstetrics and Gynaecology was held in the newly opened hospital in April 1939, and this gave the Society the welcome opportunity of having many of the leading obstetricians and gynaecologists in Britain and not a few from other countries as its guests at a reception in the Music Hall in celebration of its centenary. Five troubled months later the storm of war broke.

Now after eight years I stand here to bid you an official farewell and to hand over my duties to one who has been unanimously and with acclamation chosen by you as my successor—Dr Theodore Haultain. The feelings of regret with which I demit office are more than counter-balanced by the pleasure of welcoming as our new President one who has been my close colleague and friend for many years, and who so worthily maintains in a second generation the honour long associated with our minds with the name of Haultain.

The revival of our Society's life after such a long and testing interval cannot but be fraught for us with memories of those who were either familiar figures or famous names to us in the days which are gone but who are no longer with us. I count it my primary duty to-night to recall them briefly to your recollection.

Amongst our *Honorary Fellows* I name first one who was a dear and familiar friend of many of us, *William Fordyce*. He joined the Society in

\* Being the Valedictory Presidential Address to the Edinburgh Obstetrical Society, 13th November 1946.



1888 and in due course held the offices of Librarian, Secretary and Vice-President. In 1920 he was elected President and in 1931 received the high honour of being made one of our Honorary Fellows. Time does not permit me to refer to his contributions to the Society or to his work in the Royal Infirmary and the old Royal Maternity Hospital. That has been done elsewhere, and at this time I confine myself to saying that he was a gynaecologist of distinction, a great teacher and a great personality. But it is as a genuine, unaffected warm-hearted friend that he will live in our memories, and not less as a singer on social occasions of his own inimitable verses.

Others of our Honorary Fellows who have died include *Professor Henry Briggs* of Liverpool. The active professional life of this great obstetrician belongs to a previous generation, and all I need say is that the foundation of Liverpool's reputation in obstetrics was well and truly laid by him.

*Dr John Shields Fairbairn* of London was a man possessed of a wide and scholarly knowledge of obstetrics and gynaecology. He was gifted with a refreshing independence of mind, and an equal frankness of speech tempered by a disarming humour. By his work at St Thomas's Hospital, by his books and papers, by his service on the Central Midwives Board for England, and by his Presidency of the Royal College of Obstetricians and Gynaecologists he has made a lasting contribution to the progress and teaching of our special subjects.

*Professor Howard Kelly* of the Johns Hopkins Hospital and School in Baltimore was a man whose name will always live in the annals of gynaecology. With Welch, Halstead and Osler he was one of "the big four" who established the fame and set the standards of "the Johns Hopkins" throughout the world. He was a daring and dexterous operator and had a wide knowledge of the history of our profession. We all owe much, either consciously or unconsciously, to the magnificently illustrated books with which he enriched the literature of gynaecology.

*Professor Joseph de Lee* of Chicago was another of the American giants in our profession, and the great and beautiful maternity hospital which he erected in that city will remain as a lasting memorial of his work. To us he is best known as the author of an almost equally monumental textbook of midwifery which through edition after edition he built up into an invaluable treasury of obstetrical knowledge and instruction.

*Professor Herbert Spencer* of London was also of the race of giants. His vast experience in University College Hospital, and his wide command of British, American and Continental literature combined with his forceful personality to make him a doughty protagonist in debate. No one who ever heard him debate is likely to forget his mental vigour and forthrightness, and none who knew him will forget the essential kindness behind the brusque manner. Spencer made himself a master of medical and, in particular, of obstetrical history and has left us valuable papers on these subjects.

*Sir William Smyly* of Dublin, for long the doyen of the obstetrical and gynaecological world in Ireland, was a man to whom, by virtue of his personality and culture, honours came readily. As Master of the Rotunda Hospital he expelled the untrained midwives who used to nurse there, and was responsible for the building of the first operating theatre and the starting of the gynaecological section of that famous hospital which next summer celebrates its two-hundredth anniversary.

*Sir Comyns Berkeley* will long be remembered for his voluminous and authoritative writings and for his work on the Central Midwives Board for England. A brilliant member of the staff of the Middlesex and Chelsea

Hospitals, where he succeeded Bland Sutton, he worked out with Mr Victor Bonney the technique of the extended panhysterectomy for cancer of the cervix, and when radium came on the field he devoted much attention to its use in the same fell disease. All who knew him personally will recall his gaiety and humour, and his perennial youthfulness of outlook, as well as the staunch courage with which in his last few years he faced grievous personal trials.

*Dr Thomas Watts Eden*, who died only a few weeks ago, was one of the most distinguished Edinburgh graduates who kept the great reputation of our University honoured and unsullied in "the citadel" of London. He was a master of clear and polished English both in speech and writing, and his *Manual of Obstetrics* and the two books on gynaecology which he edited with Mr Cuthbert Lockyer were outstanding and authoritative additions to the British literature of our profession. He was a member of the staffs of the Chelsea, Queen Charlotte's, and Charing Cross Hospitals, and his work did much to enhance the prestige of each of them. With a statesmanlike clarity of vision Dr Eden united a personal simplicity and friendliness which commanded universal respect and affection.

Of our *Ordinary Fellows*, we have lost thirty-three to my knowledge. The most senior was *Dr Keppie Paterson* who joined the Society as long ago as 1882 and became Vice-President in 1913. Up to the end of a long life he maintained a lively interest in all matters obstetrical and was a faithful attender and a frequent speaker at our meetings.

*Dr Oliphant Nicholson* became a Fellow of the Society in 1900, and in 1933 he was elected to the President's chair. He was a man of distinguished ability, with scientific interests in both medicine and midwifery. For a number of years he was an Assistant Physician to the old Royal Maternity Hospital, and it was there that he made the observations on the theoretical connection between hypo-thyroidism and eclampsia with which his name is associated.

Another veteran Fellow was *Dr Robert Thin* who joined the Society in 1891. He was a man of wide reading and culture, greatly beloved and still sadly missed by a vast circle of patients.

*Dr Andrew Graham Ritchie* was yet another of our Fellows whose death left a large circle of his patients with a feeling of personal bereavement. With his father's practice he inherited also his father's lively interest in our Society at which he was a faithful attender and a not infrequent speaker.

The death of *Professor James Hendry* of Glasgow has been a heavy blow to the University and to the profession in that city, and here also he will be greatly missed. His active interest in our Society led to his being appointed Vice-President in 1936 and President in 1937. He made several valuable contributions to our *Transactions* and took part in many of our discussions, to which he brought a singularly well-ordered mind with a wide practical experience in obstetrics and gynaecology.

The mists of the Cairngorms still shroud with an impenetrable veil of mystery the death of *Dr William Hamilton* of Roslin. From 1924, when he joined the Society, he showed a keen interest in all our obstetrical work. Hamilton was a man who thought things out logically for himself, and he had a great gift of clear exposition of his opinions. His character commanded great respect from all his fellows, but he was in some ways a lone figure, and there was something almost appropriate in his strange and solitary end.

Two other country practitioners who were active supporters of the Society were *Dr David Huskie* of Moffat who thought little of driving a hundred miles to our meetings although he rarely spoke at them, and *Dr Lachlan*

*Grant* of Ballachulish. Many of you will remember the practical contributions which Dr Grant made to the Society, and no one had a more intimate understanding of the obstetrical difficulties which the country doctor is called upon to face, or a greater zeal in trying to apply to them the best standards of practice.

Other Fellows of the Society who have died and whom I shall just mention by name are *Dr Alexander* of Elgin, *Dr E. F. Armour*, *Dr R. W. Beesley* of Bolton, *Dr John Cumming*, *Dr J. M. Dewar*, *Dr Elliot Dickson* of Lochgelly, *Dr Fitzgerald* of Manchester, *Dr L. P. M. Gardner*, *Dr Wilton Johns*, *Dr Hamilton Langwill*, *Dr Morison McIntosh*, *Dr Malcolm McLarty*, *Dr Mary McNicol*, *Dr J. Hally Meikle*, *Dr George Melville* of Musselburgh, *Dr Kenmure Melville*, *Dr Mitchell* of Malvern, *Dr Orr* of Eccles, *Mr Hogarth Pringle* of Glasgow, *Dr T. W. E. Ross*, *Dr Robert Stewart*, *Dr Robert Stirling* of Perth, *Dr J. L. Thompson* of Victoria, Australia, *Dr Isobel Venters*, and *Dr A. Murray Wood*. And, lastly, we deplore the loss as a result of wounds received in that glorious epic battle of "the retreat to Dunkirk" of one of our youngest Fellows, *Dr J. K. Sutherland*. His death was a personal grief to myself because he was one of the most outstanding of the distinguished group of young men and women whom I have had the honour to have associated with me as house surgeons. Dr Sutherland was a man of great promise, and in his death *pro patria* obstetrics and gynaecology, to which he was proposing to devote his life, have suffered a real loss.

From this pious but melancholy duty of remembrance I pass to my valedictory remarks, and naturally enough they also concern what is past.

It is forty-three years since I became a Fellow of the Society, and that period seems to justify my indulgence in the usually enervating practice of retrospection. I have spent some time looking back over our *Transactions* for these years to see if they reflected the progress of obstetrics and gynaecology in the last half-century, but, curiously enough, they do so only in a patchy manner which is not helpful to my purpose. There is in them, however, one address to which I found myself returning time and again—Dr J. W. Ballantyne's presidential address in 1906. There cannot be more than two or three, if as many, here present who share with me the recollection of listening to it. The Society met in those days in the Goold Hall in St Andrew Square. Later, as many of you will recall, we moved to the New Gallery in Shandwick Place, and finally to these rooms of the British Medical Association.

I well remember how startled the audience was when the new President of 1906, one of the most sedate and to outward appearance prosaic of men, cast his address in a form which was not only unique in our annals but even partook of the nature of highly imaginative fiction. Ballantyne told us the story of a telephonic conversation which he held late one night, through the medium of some fourth dimensional exchange, with the President of our Society in 1940. Admittedly his dream lacked the amazing incoherence and the fantastic irrelevance of the dreams which we all experience on occasion, but it served his purpose which was to make his successor-in-office, four and thirty years later, describe as matters of recent history or of current

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practice some of the hopes and aspirations which he himself cherished. And if some of what Ballantyne forecast in this ingenious fashion savours of the fantastic, that was merely a deliberate and whimsical concession to the dream-form—or as he, with his love of long Greek words would have called it, the oneirophantic form—of his remarks.

In the latter part of his address there is a passage, very characteristic of the earnest and good man that Ballantyne was, in which he raises the problem of cancer. The President of 1940 is cautious in his reply, but directs attention to what he calls "a curious parallelism between great philanthropic movements and noteworthy life-saving and pain-relieving discoveries." He instances as an example the abolition of slavery, which was followed some years later by the discovery of anæsthesia. Ballantyne then asks, "Was there any great philanthropic advance pending in 1906 or soon thereafter, which made it possible for the discovery of the cause and cure of cancer to take place as a corollary thereto?" The President of 1940 replies, "The greatest boon that mankind could voluntarily bestow upon itself would be the abolition of war, would it not?" Well, Ballantyne lived till 1923, so that he saw one great world war postpone the consummation of this pious aspiration. But is there not something pathetic in the thought that yet another and more terrible world war was to follow and to bring it about that in the year 1940 this Society was in a state of suspended animation and its President had consequently no opportunity to communicate with his spirit? I have felt, however, that communication between us ought to be re-opened, and perhaps this belated address to you may be accepted as such!

To most of our younger Fellows Ballantyne is only a name honourably associated with the subject of antenatal care, of which in his later years he was the great apostle. It may, therefore, be interesting if I tell you of the rather devious way by which he became converted to the far-reaching truth and importance of that gospel.

There was nothing dramatic about it like the conversion of the great Apostle to the Gentiles. It was rather more like the picturesque story of that Apostle's earlier namesake, Saul the son of Kish, setting out to find his father's asses and, having completely failed to do so, returning home as the anointed heir to a kingdom and numbered amongst the prophets.

The facts as I remember them are these. Ballantyne's great interest was in foetal pathology and teratology, and his books on those subjects are encyclopædic in their learning and still authoritative. He conceived the idea that something might be done to prevent some foetal abnormalities and diseases by treatment of the mother during pregnancy; and it was to enable him to carry on his observations that Dr Freeland Barbour, a wealthy member of the staff of the old Maternity Hospital and himself a distinguished contributor to our knowledge of the anatomy of labour, endowed a bed in the hospital, which he named the Hamilton bed in memory of Alexander and James

Hamilton who, father and son, between them occupied the Chair of Midwifery in our University from 1780 to 1840. This bed was set aside for the *study* of disease in pregnancy in 1901, and was the first bed in the United Kingdom and probably in the world set aside for this specific purpose.

Meantime a collateral advance was being made by Dr Haig Ferguson, who for many years had cared for the health of the young women, illegitimately pregnant, who were the inmates of what was then called the Lauriston Home. Being impressed by the apparent benefits which accrued to these patients and their babies from the careful antenatal supervision which they received during the later months of pregnancy, Dr Haig Ferguson arranged in the early years of this century to extend a similar supervision by means of an out-patient clinic to the married women and others who intended to enter the hospital for their confinements. In a very few years this novel venture became a busy clinic, and in 1915 it was incorporated as a regular part of the hospital's work, and Dr Ballantyne was persuaded, despite some reluctance on his part, to relieve Dr Haig Ferguson of its general supervision. Thus from these two convergent movements there developed the general plan of antenatal care, which has since spread throughout the world; and it should be a source of legitimate pride to us to remember that our old hospital was the cradle in which the most important advance in modern obstetrics was nurtured. But the curious, almost paradoxical, fact remains that in the first few years after the establishment of the Hamilton Bed Ballantyne's interest remained focussed on problematical benefits to the foetus, and it was only gradually that he became seized with the greater and more immediate benefits accruing to the mother. Once he had appreciated these results, however, his enthusiasm was quickly kindled and he became, as I have said, the first great apostle of the new gospel.

In the circumstances which I have related it is not surprising to find that Ballantyne's address in 1906 is more taken up with questions like the falling birthrate and the wastage of antenatal life than with the maternal benefits which have actually formed the most obvious harvest of antenatal supervision. He had not yet clearly visualised that aspect of the matter, but the idea was evidently germinating in his mind; for he makes the President of 1940 describe how, subsequent to 1906, the "hygiene of pregnancy began to be studied with an enthusiasm and thoroughness never before arrived at. Patients were encouraged to consult their medical attendants regarding the rules of health in pregnancy and the latter were prepared to give the advice sought."

We must not conclude from this quotation that our predecessors of half a century ago entirely neglected the antenatal period, but it is true that it was unusual in those days for the doctor to be informed of the existence of pregnancy unless some serious symptoms such as excessive vomiting or marked pre-eclamptic manifestations or a

hæmorrhage occurred. Otherwise he was informed only in the later weeks that his services would be required in the near future. To quote Ballantyne's imaginary President of 1940 again, "The obstetrician of 1940 finds it difficult to understand why his brethren of the early part of the century paid so much attention to the one month of the puerperal period and so little to the nine months of pregnancy. To him the time of preparation for labour was not less but more important than the time of recovery from the effects of labour, for he found that if the former was normal the latter was little likely to be pathological."

What I have said and quoted does much less than justice to Ballantyne's brilliant, learned and intriguing address, but my present duty is to attempt to reply to the challenge inherent in it. What shall I say to-night to Ballantyne's ghost? How can I best explain to the President of 1906 the progress of obstetrics in the last forty years? So far as Edinburgh is concerned the answer is simple. For since in 1906 Ballantyne's "imagination bodied forth the forms of things to come," it were only right for the retiring President in 1946, even though lacking "the poet's pen," to give them "a local habitation and a name." And what habitation and what name more appropriate than "The Simpson Memorial Maternity Pavilion," which now commemorates the greatest of our obstetricians more amply and worthily than did the great little hospital with which Ballantyne was so familiar in his earthly life?

If, then, I may evoke Ballantyne's spirit without unduly disturbing his rest, let me invite him to inspect the new hospital with me. We begin at the Almoner's office, where we sit down for a few minutes, and in order to let him attune himself once more to mundane conditions I talk to him about the design of the new hospital; about the expansion of our clinical teaching, pointing through the windows to the students' hostel which was opened in 1933; and about such wider matters as the foundation in 1929 of the Royal College of Obstetricians and Gynæcologists and its great subsequent progress. As soon as I consider him fully interested I begin to feed him with facts and figures. For in his lifetime Ballantyne devoured statistics, and lulled himself to sleep most effectively with the poppy of White Papers and the mandragora of Blue Books. I tell him that whereas the maternal mortality for Scotland in 1906 was 5·4 per thousand live births, it had been reduced by 1945 to 2·86; that for the first half of 1946 it stood at 2·25, and the Registrar-General cherished the hope of seeing it soon drop below the death-rate for non-pregnant women in comparable age-groups. I cheer him by the information that the infant mortality rate, which stood at the deplorable figure of 115 per thousand live births in 1906 had been halved, and in 1945 had reached the record low figure of 56 per thousand. I give him the comfortable assurance that the gospel of antenatal care had developed much as he had foreseen, that its practice has become the general rule amongst civilised peoples, and that it is generally recognised as constituting the most outstanding



advance in obstetrics of the first half of the century. Lastly I tell him of the investigations into maternal mortality and of the Scottish Maternity Services Act of 1937 which resulted from them and which is now in general and beneficial operation.

When the profound significance of all these facts and figures has sunk in, my ghostly visitor and I cross over to the Antenatal Department. All who remember the dark and cramped basement in which the antenatal clinics were conducted in the old hospital will appreciate the gratification with which he flits through the spacious clinic watching the white-robed doctors giving antenatal attention to scores of patients. Or if it be the forenoon when we pay our visit he sees the postnatal clinic in operation, and I tell him how this branch of our work has developed as a natural corollary to antenatal care, and enables us to obviate many of the minor sequelæ of parturition, such as uterine displacements, cervical catarrh and the like.

In the course of a brief but encouraging inspection of the Infant Welfare corner I tell him of the peaceful penetration of the pædiatric specialists into our hospital work, and of how, with their help, we are setting our course towards a complete integration of the maternity and the infant welfare services which will guard and maintain the safety and well-being of both mother and child before, during and after birth. That, indeed, might be taken as the briefest summary of the progress we are making.

Midwifery, as I see it, is in a transition period. Behind us we have the bad old days when, in the absence of any adequate or widespread antenatal care, complications had to be treated as and when they arose, and when consequently the obstetrician was often faced with a conflict between the interests of the mother and those of the child. Naturally the former had always the preference, and many of the methods of treatment were associated with a distressingly high infant mortality.

The present trend of obstetrics is characterised by a gradually increasing avoidance of complications by means of antenatal care generally, and by accurate X-ray pelvimetry as merely one specific example out of many; by conservative treatment when possible—and here one might instance the modern treatment of cephalo-pelvic disproportion and of placenta prævia; and by the use of the lower segment Cæsarean section in many cases in which conservatism is not possible. Taken together these all make not only for the safety of the mother but for the greater safety of the child, and the increasing emphasis on the safety of the child is one of the most noteworthy features of present-day obstetrics. The efficiency of a maternity hospital is now assessed not merely by its maternal mortality rate but by such criteria as the foetal death-rate in breech deliveries in primiparæ.

Before us we have the days when this trend will have reached its fulfilment, and forty years hence my successor in this office will perhaps evoke both Ballantyne's ghost and my own, and tell us of a highly

organised and efficient specialist maternity service spread over the whole country under which, with the help of an enlightened public opinion and the compulsory notification of pregnancy, every woman will be getting really adequate antenatal, intranatal and postnatal care, and both maternal and infant mortality rates will have been brought to the irreducible minimum.

With these generalisations in mind my ghostly companion and I now pass to the large sunny antenatal ward. It is a summer day, the great French windows are wide open and the chaffinches are flitting in and out intent on a profitable search for suitable provender for their infant welfare department. I point out to my companion the Hamilton Bed, now merely the senior member of an all-too-small group of twenty-five. I tell him that "the Simpson" now has an average complement of 140 beds, but that on occasion it has sheltered more than 190 actual or expectant mothers, and therefore the cry is still "more beds." For the growth of institutional midwifery is largely a phenomenon of our days—the product of the housing problems following two long wars and the social revolution which they have accelerated. Whether it is to be included amongst the advances of midwifery may possibly be debatable, but personally I am disposed to regard it as such.

As we pass from bed to bed my friend observes that we still have to deal with most of the conditions that used to occupy our predecessors' attention in 1906. The most striking absentee is the miserable victim of serious hyperemesis. It gives me great pleasure to tell him that this condition is now a comparative rarity; that for some years back I have not had a case of grave hyperemesis to demonstrate to my students; and that teaching colleagues in other centres tell the same story. In the five years 1923-28 we had in our hospital an average maternal mortality in cases of hyperemesis of no less than 13·4 per cent.; by 1939 it had been reduced to 2·7 per cent.; in the first five years of the war it fell to 0·6 per cent.; and since 1940 no death from this condition has occurred in the hospital. In my view this improvement is to be attributed to the growing recognition of the importance of antenatal work, doctors sending their cases to hospital at an early stage while the condition is easily curable. There has also been a fall in the incidence of such cases during the war years, and, being a firm believer in the predominance of the psychological, or, as it would now be termed, the psychosomatic factor in this disease, I attribute that to the great and enforced pre-occupation of the expectant mother's mind with objective matters arising out of war-time conditions. If I am right, we may expect to see an increased incidence when the austerity of the present "peace" diminishes.

"But what of eclampsia?" Ballantyne's ghost enquires, for the conquest of this fell disease was one of the brightest hopes of the pioneers of antenatal care. I fear my answer disappoints him, for although there is certainly less eclampsia than in his day, yet it is still

second only to sepsis as a major component of the maternal mortality statistics. It is difficult to summarise the progress we have made. We have rid ourselves of some outmoded shibboleths such as the "albuminuric of pregnancy"—a term that, in his valuable book, which is by its merits and its world-wide influence the greatest monument dedicated to Ballantyne, Professor F. J. Browne stigmatises as having done "more than anything else to hinder the early diagnosis of pre-eclamptic toxæmia." We have been concentrating more on the hypertensive aspects of the condition, and on such problems as increased capillary permeability than on the search for a specific toxin; and by earlier diagnosis and more prompt and general hospitalisation we are tending to prevent the "hypertensive encephalopathy" which probably lies behind the convulsive phase of the disease. But does all that represent progress or merely a change of direction? In the last five and twenty years we seem to have settled into a sort of undisciplined trench warfare against the toxæmia of pregnancy, in which any private who wishes to make a little noise fires his rifle with about as much effect as a squib, while every now and then one of the big guns hurtles a shell at what he or she or it thinks is a centre of the enemy's communications. Monographs are issued which are little more than descriptive catalogues. Even an organised attack by a group of American physicians under skilled and experienced leadership makes little real impression. It is all like so much blind reconnaissance work. What we need is something corresponding to the airborne observer, who can spot the real heart of the enemy's activity and direct our attack upon it.

But metaphors if pursued too closely can be as dangerous as a hand grenade, so I hastily change the subject, and, to mitigate his disappointment, lead my ghostly companion to the bed of a diabetic woman. Ballantyne lived to see the discovery of insulin, but not to see it abolish in great measure the erstwhile terrors of the association of diabetes and pregnancy. It was in 1909 that Whitridge Williams recorded sixty-six such cases with a maternal mortality of 27 per cent. at or shortly after delivery (mostly in coma), and a further 23 per cent. mortality within two years subsequently. In 1938 I recorded<sup>1</sup> that in our hospital we had had 23 cases with no maternal death in the preceding ten years. Since then we have had 29 more cases, making a total of 52 with no maternal death.

It is, however, not the same story in regard to the baby. In Williams' series the foetal mortality was 41 per cent. In our series it was 35 per cent. for the first 23 cases and 17 per cent. for the last 29, making an overall foetal mortality of 25 per cent. Putting aside foetal death from birth trauma associated with undue size of the foetus, the cause of foetal death in diabetes is still obscure, but it seems clear that it is not due to hypoglycæmia. Recently H. C. Miller<sup>2</sup> in America has investigated the obstetric histories of diabetic women, and has found that for several years before the appearance of the diabetes

there was a significant increase in foetal and neonatal deaths among them. But what is more remarkable is that the pathological conditions found in infants born of diabetic mothers—macrosomia, cardiomegaly, hyperplasia of the islands of Langerhans and of the adrenals, etc.—have all been found in infants born several years prior to their mothers' development of diabetes, "suggesting a high degree of sensitivity in the human foetus to the etiological factors, whether endocrine or otherwise, that ultimately produce diabetes."

Thus, talking shop, we drift round the ward with a few words about such familiar conditions as heart disease, anæmia and disproportion. A case of pyelitis calls for reference to the work of Baird and others on its etiology and on the newer urinary antiseptics, but I observe my friend's eyes kindle when we come to a case of threatened or of habitual abortion. He listens with rapt attention as I am privileged to unfold the amazing story of the new physiology of the female reproductive organs. Even those of us to whom the process of revelation has come bit by bit over some five and thirty years, giving us more knowledge in that single generation than had been reached in all time past, have perhaps lost some of our sense of wonder and gratitude; while the younger among us, who learned it as students, probably do not fully appreciate how recent it all is, and what a stupendous and revolutionary contribution to our knowledge and our resources it forms. But the President of 1906 knew nothing of all this, and to his ghost it is an astounding narrative. For it all began in 1908 when Hitschmann and Adler first demonstrated the cyclical nature of the changes in endometrial structure. This was followed by the work of Schroeder and others which established the histological and chronological correlation of the ovarian and the endometrial cycles. Then came Allen and Doisy's discovery of the oestrogenic hormone and a few years later Corner's discovery of progesterone. To crown this came the memorable work of Aschheim and Zondek who taught us to refer with assurance our doubts as to the existence of an early pregnancy to the arbitrament of young female mice, thereby elevating those despised rodents to the rank of obstetrical consultants, and establishing the primacy of the anterior lobe of the pituitary over the functions of the ovary. The comment of Ballantyne's ghost upon all this is in Dominie Sampson's one word—"Pro-di-gi-ous!"

I now conduct our friend to one of the lying-in wards where he expresses delight with the general lay-out of the spacious sunny rooms. He tends to loiter in the nursery, where he enquires if we have found the cause of premature births. I have to confess that we have not, but that mass experiments have suggested, although perhaps not proved, the importance of diet and particularly of vitamins in this connection. This calls for some explanation, for in 1906 practically nothing was known of these vital factors, and even in 1923 when Ballantyne died our knowledge was confined largely to the facts that

conditions such as night-blindness, beri-beri, scurvy and rickets were associated with dietetic deficiencies. Five years were to elapse before Szent-Gyorgyi got on the track of vitamin C, but not knowing what it was, proposed to call it "ignose," and, when that term was rejected suggested as an alternative "godnose"!

My little dissertation on vitamins leads me to mention the work of Warkany and Nelson<sup>3</sup> who found that in rats fed on a rhachitogenic diet, with viosterol added to prevent rickets, a third of the offspring were born with skeletal abnormalities, which could be prevented if liver were added to the diet. Since Ballantyne's great hobby was the study of foetal abnormalities and his greatest hope that light might be thrown on their causation which would lead ultimately to their prevention, this reference rivets his attention. Then I think I give him a real thrill, which would have been impossible for the President of 1940. For it was only in 1945 that McAlister Gregg and Carruthers<sup>4</sup> in Sydney published the results of an enquiry by the Department of Public Health in New South Wales into the results upon the child of a mother's having suffered from rubella in the early months of pregnancy. These results and others<sup>5</sup> that are now coming forward all seem to show that if a woman contracts rubella in the first two months of pregnancy there is a 100 per cent. certainty of her giving birth to a child with congenital defects, and a 50 per cent. chance if she acquires the disease as late as the third month.\* The defects noted are principally congenital cataracts, cardiac lesions and severe deafness leading to deaf-mutism. It is legitimate to assume that the disease-virus passes readily through the placental barrier and affects the delicate cells of the young embryo.

This naturally leads me next to descant briefly on the Rhesus factor. You can readily imagine my companion's interest at hearing that we have learned the cause of such conditions as icterus gravis, hydrops foetalis and congenital hæmolytic anæmia, and are hopefully expecting that in due course the immunologists will find the means of prevention. These recent advances are surely the first glimmerings of the dawn over that vast and dark *terra incognita* of foetal pathology, which occupied so much of Ballantyne's thought.

During our inspection of the labour wards my visitor surprises me by asking, "Why are all the nurses and students wearing masks over their mouths and noses?" and I realise that it was only in 1931 that Smith of Aberdeen first focussed our attention on the importance of "droplet infection," and in 1935 that the Colebrookes clinched the matter and raised the Lancefield Group A hæmolytic streptococcus to the position of "Public Enemy No. 1" in childbirth.

In the theatre I tell my friend of the great advantages derived from the lower segment technique in Cæsarean Section—of how it has enabled us to widen the indications for the operation and at the same time to increase both its immediate and remote safety. The question

\* It is probable that further observations will materially reduce these percentages. See *Brit. Med. Journ.*, 23rd November 1946, p. 778.

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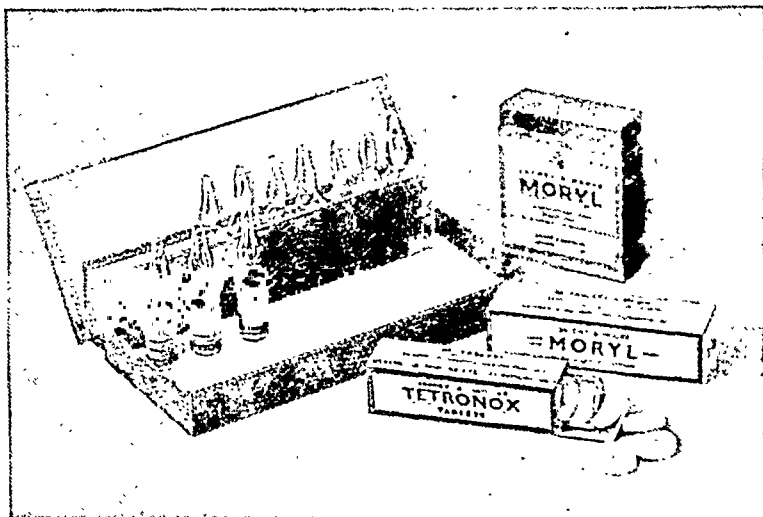
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of anæsthesia and of obstetric analgesia also crops up, and we spend some time discussing the remarkable developments in this branch of surgery, with their increased comfort, safety and efficiency.

We then enter the lift to go up to the segregation wards, and I am conscious that we ascend with unwonted speed, as if some supernatural process of levitation were at work. But we arrive safely and find most of the beds on the balconies, and the patients enjoying the therapeutic influences of sunshine and the open air. I notice my friend gazing rather wistfully over the beautiful and once so familiar view of the Braids and the Pentland Hills, but he comes back to the more immediate object of his visit and questions me on the treatment of puerperal infection. Here, sitting in the sunshine, "faint yet pursuing," I have another great story to unfold to my inexhaustible companion—first of our increasing understanding of the bacteriological causes of puerperal infection, and then of how this achievement was rewarded by the great discovery of prontosil by Domagk, and of the immense subsequent evolution of the sulphonamide group of drugs. Finally there comes Fleming and Florey's fairy-tale of penicillin.

Once again it seems to me that Dominic Sampson's immortal comment is forming itself on the lips of Ballantyne's ghost, but he checks it. "Mr President," he says, "what you call time is passing, and I must return to my rest. I gladly forgive you for disturbing it, for it will now be all the sweeter for the knowledge that obstetricians have progressed so far towards the mastery of that greatest danger of childbirth, puerperal infection; that they are setting themselves so definitely to save infant as well as maternal life; that they are still pursuing the quest for the relief of pain so dramatically launched by our great master almost a century ago in this very city; and that the first furrows are being ploughed in the wastes of foetal pathology. I cannot recall any corresponding period of years in which obstetrics has made more fruitful progress or has received such great gifts from the physiologist and the pharmacologist. I am happy to think that I had in my time a share in sowing the grain which you are now beginning to garner. But tell your colleagues everywhere to remember the apostolic injunction not to weary in well-doing for in due season they shall reap if they faint not.

"Mr President, will you please give my best wishes to the old Society, and my cordial congratulations on its having passed its hundredth anniversary without any signs of senility? And now, my friend," says Ballantyne's ghost, "it would advantage me nothing to go down all these long stairs again. So let me just say—for myself certainly, and for you also if I sense the situation aright—Thank you and—Good-bye."

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## PROLAPSED INTERVERTEBRAL DISC \*

By G. L. ALEXANDER, F.R.C.S. (Ed. and Eng.)

With the assistance of

Dr S. BATKIN and Dr H. MASLOWSKI

THE intervertebral discs consist of a tough fibrous annulus peripherally, enclosing the fibro-gelatinous nucleus pulposus, and are limited above and below by the cartilaginous plate covering the apposed faces of the vertebral bodies. The discs impart to the spinal column a high degree of flexibility and act also as shock absorbers when force is applied in the long axis of the spinal column. On occasion the annulus fibrosus yields or ruptures. The yielding may occur all along the annulus, increasing as age advances, and, if ossification extends into the attachment of the annulus to bone, the "lipping" characteristic of spondylitis becomes radiographically apparent. Rupture of the annulus, as seen generally in younger subjects, seems most often to occur posteriorly, just lateral to the posterior common ligament, and the protrusion comes into relation with nerve roots in their epidural course as they emerge from the theca. The lumbar disc protrusion may displace the nerve root medially or laterally as well as backwards. Two roots may be implicated by one lateral protrusion of the disc; as an example, the first sacral root may be displaced by a lumbosacral disc, and the fifth lumbar root may also be nipped as it passes out through the intervertebral foramen at that level.

The rupture may occur at or near the midline and the theca as a whole is displaced posteriorly, with the result that tension is exerted indirectly on nerve roots in their dural sheaths bilaterally; more than one pair of roots may thus be under tension.

The more extreme protrusions, especially the paramedian type, are liable to cause compression of the cauda equina, and it is of prime importance to recognise and treat those cases promptly; they should be regarded as surgical emergencies.

We have no real knowledge of the underlying factors which predispose to rupture of the annulus fibrosus, except perhaps in relation to pregnancy, when some temporary softening of pelvic connective tissues is physiological. The majority of the patients are well-developed adults in the third and fourth decades, apparently in good health. The parous female patients often give a history of transient symptoms characteristic of ruptured intervertebral disc late in pregnancy or in the puerperium.

\* Read at a meeting of the Edinburgh Medico-Chirurgical Society on 1st May 1946.

Concerning the type of backstrain associated with rupture of lumbar discs, there seems usually to be an element of flexion at the moment of strain, though occasionally a hyperextension movement is described as having been responsible. A heavy fall in the sitting position is a common precipitating injury ; often no immediate disability is noticed, but the lumbar backache comes on days, weeks, or months later. Many patients indeed can recall no incident of strain ; many of them are subjected to habitual backstrain in their daily work.

Love and Walsh have shown graphically the relative incidence of rupture of the intervertebral disc at different levels of the vertebral column. Our series has shown a still greater preponderance in the lower lumbar region and we have had so far no instance in the thoracic region.

As neurological surgeons we see of course a fair proportion of selected cases, and we are therefore not in a position to evaluate the frequency with which "sciatica" is due to ruptured intervertebral disc. We believe it to be rather high, however.

### LUMBAR DISCS

Typically the syndrome consists of lumbar backache followed by referred sciatic pain, but this sequence is by no means invariable.

The lumbar backache was the first symptom in 52 per cent. of our cases. Backache and sciatica occurred simultaneously in 16 per cent., and sciatic pain preceded the backache in 32 per cent. Frequently the backache is subsiding or has disappeared before the referred sciatic pain develops. Many patients who consider themselves free of backache will admit to a periodical transient stiffness in the lumbar region on rising from bed, or after prolonged sitting.

The chief characteristic of the referred pain is its mono-radicular quality. Two nerve roots may be implicated, as noted previously, but even so the main disturbance can usually be identified with one particular nerve root. The pain is very commonly increased momentarily under conditions which raise intracranial pressure, as in sneezing, coughing, and straining. It is inferred that this exacerbation is caused by a fluid distension of the arachnoidal sleeve which invests the nerve root for a considerable distance out from the theca.

We have had one patient with cerebral tumour and with a ruptured lumbar disc syndrome whose sciatica ran parallel with his several phases of intracranial hypertension over a period of years. Any posture, such as stooping, which exposes the sciatic nerve to stretch, increases the root-pain, and this fact is the basis of the straight-leg raising test, commonly referred to as the Lasegue test, albeit the test described by Lasegue differs somewhat, though the effect is similar. Another symptomatic feature is the relief of pain often afforded by getting up and walking around for a time.

Intermittent numbness and tingling of mono-radicular distribution

are nearly always later developments in the syndrome, if they appear at all.

It is appropriate now to consider the motor, sensory, and reflex changes associated with dysfunction of the nerve roots most commonly involved by prolapsed lumbar intervertebral discs.

The *fourth lumbar* dermatome traverses the antero-lateral aspect of the thigh obliquely, includes the skin overlying the outer half of the patella, and, extending down over the subcutaneous surface of the tibia, includes also part of the medial aspect of the foot. The quadriceps muscle is weak and the knee jerk diminished. We have had two cases exhibiting those findings due to rupture of the disc between third and fourth lumbar vertebræ, confirmed at operation.

The *fifth lumbar* dermatome occupies the lateral aspect of the thigh, includes the skin overlying the anterior tibial group of muscles, crosses the dorsum of the foot obliquely, and terminates in the medial two toes. Gluteal muscles, and especially dorsiflexors of ankle and toes, are weakened, inversion of the ankle is poor. The ankle jerk is preserved.

The *first sacral* dermatome is to be found postero-laterally on the thigh, on the lateral aspect of the leg, and includes lateral malleolus and lateral border of foot; it terminates in the outer three toes. Hamstrings and glutei are affected and the plantar-flexors of foot and toes are conspicuously weakened. Eversion of the ankle is poor. The ankle jerk is diminished or absent. Some wasting usually accompanies the motor impairment in those several muscle groups and fasciculation also occurs in the muscle-bellies. This latter phenomenon used to be thought pathognomonic of disturbance in the anterior horns of the spinal cord but it is evident that it has a wider significance.

Examination of the spine may reveal no abnormality apart from some limitation of flexion in the lumbar region when tested with the patient standing; this improves considerably in the sitting position, with sciatic nerve relaxed. Most cases show some flattening of the normal lumbar lordosis, and a tilt of the trunk towards or away from the affected side. This latter we prefer to describe as a tilt of the trunk rather than a scoliosis, for it is characteristically an abrupt lateral angulation in the lower lumbar region. We believe that the direction of tilt of the trunk may be determined by the lie of the protrusion of disc relative to the nerve-root, and that the tilt tends to occur in that direction which provides the greater relaxation of the affected root (Fig. 1).

Pressure over the affected interspace just to one side of the spinous processes with the examiner's thumb, the patient being prone and relaxed, yields valuable information in many cases. If this manœuvre causes reference of pain to the buttock, thigh, or even more distally, and if it is elicited only on the affected side and at a level compatible with the other findings, then one can diagnose with confidence the



FIG. 1.—Possible mechanism determining the direction of tilt of the trunk. (See text.)

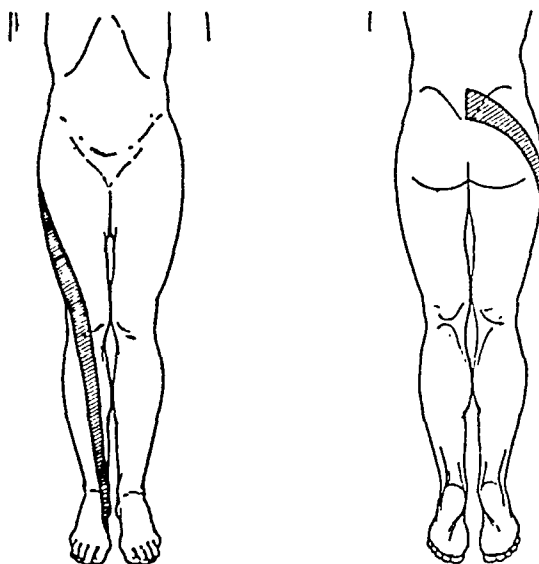


FIG. 2.—Average distribution of the fourth lumbar dermatome.

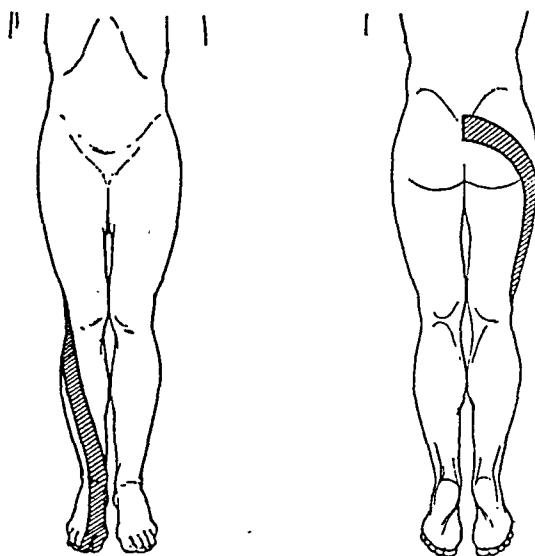


FIG. 3.—Average distribution of the fifth lumbar dermatome.

presence of a prolapsed intervertebral disc. This is, we think, the only single sign characteristic of prolapsed intervertebral disc, and it is therefore important.

The straight-leg raising test, carried out with the patient recumbent, stretches the sciatic nerve and causes reference or aggravation of pain down the limb. It is indicative of lumbosacral radiculitis, with or without the mechanical factor of a prolapsed disc. The effect is increased by dorsiflexing the foot, and even the minute additional tension imparted by flexing the patient's neck causes a further exacerbation of pain in some cases.

It is often useful to carry out sensory examination with the affected limb elevated as in this test, just short of the threshold for increased

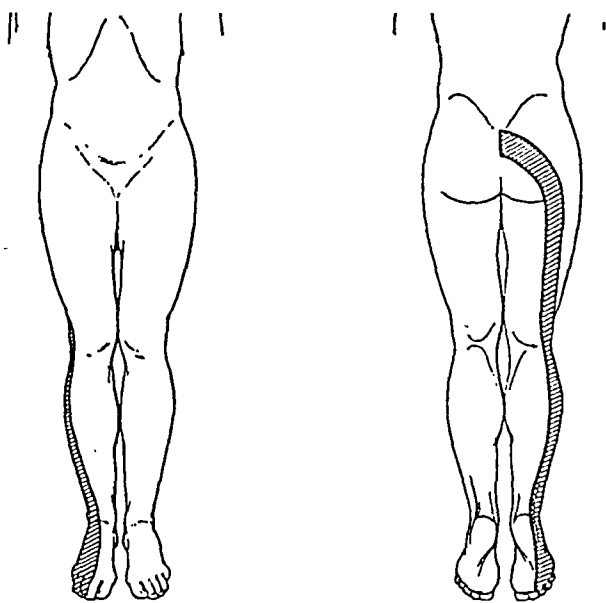


FIG. 4.—Average distribution of the first sacral dermatome.

pain, and in this manner an indeterminate sensory loss may be intensified so that it can be identified with a particular dermatome.

Some tenderness in the upper part of the sciatic nerve is common, indicating that the neurological disturbance is often of the nature of a radiculo-neuritis. In a few of the early cases we opened the dura and were able to view the swollen and congested lumbar nerve-root. This congestion and swelling always extended up beyond the limit of the operation field and may indeed have extended as far proximally as the cord. It is not difficult, therefore, to accept the evidence of a similar distal spread of the reaction into the sciatic nerve. If there is evidence of a more extensive neuritis in the lower limb the diagnosis should be reviewed in favour of a purely inflammatory radiculo-neuritis.

Radiological examination of the spinal column often gives assistance in localising diagnosis, but often the lumbar region appears quite

normal. The lumbosacral interspace in lateral view is frequently relatively narrow in normal subjects, but, if one of the interspaces at a higher level is out of series with its neighbours, due attention must be paid to the fact.

Contrast radiography was abandoned by us very early; indeed, only the first four cases of the series were so investigated. We had some doubts about the innocuousness of remnants of lipiodol persisting indefinitely in the subarachnoid space; this attitude was later substantiated when we had to reopen two of these cases on account of chronic arachnoiditis. In addition it very soon became apparent that the lumbar disc syndrome presented sufficiently typical features for a diagnosis to be made with fair certainty on clinical evidence alone. In the year 1942 the clinical diagnosis was verified at operation in 93 per cent. of the cases, and by 1945 this had increased to 96 per cent. The cerebrospinal fluid is normal or shows only slight increase of cells and total protein. The average in our series was 50 mg. per 100 c.c. for total protein (normal 30 mg. per 100 c.c.), and cells averaged 2 per cu.mm., with a maximum of 7. Marked deviations from those figures call for a reconsideration of the diagnosis.

## DIFFERENTIAL DIAGNOSIS

*Primary Radiculitis* without pathology of the disc provides the main problem in differential diagnosis, and this is not surprising because rupture of a lumbar intervertebral disc causes a radiculitis. The ætiology of the purely inflammatory radiculitis is not certain, but until further evidence is forthcoming it can reasonably be ascribed to a virus infection. Usually there is a moderate lymphocyte increase in the lumbar cerebrospinal fluid—10 to 30 cells perhaps. Recumbency gives some symptomatic relief as with disc cases, and this may well be due to diminished intrathecal and epidural venous pressure in the horizontal position. In contrast, however, the day by day lessening of pain with rest tends to be less satisfactory and consistent in cases of primary radiculitis. Observation over a week or two often demonstrates the associated neuritis extending distally in the lower limb and concurrently the condition may spread to affect the opposite side. In some cases the radiculitis may have substantially subsided while the neuritis is still acute distally; as one patient from the North put it, "The pain cam' in at my hench and ginged oot at my taes." Finally, the patient with a pathological disc is likely to give a history of several attacks of disability recurring sooner or later after resumption of work.

*Spondylolisthesis* can cause backache and sciatic pain which is practically indistinguishable from that due to prolapsed lumbar disc. Faulty alignment of the spinous processes is commonly apparent clinically and of course X-ray films give conclusive evidence. Our experience so far in a limited number of those cases indicates that

prolapse of the contents of the disc does not occur. The root-compression seems to take place at the margin of the prominent vertebral body.

Three cases of *tuberculosis* of a lumbar disc and adjacent vertebral bodies have come to our notice. They were young adults presenting a syndrome simulating that of prolapsed lumbar disc. Lumbar backache rather dominated the picture and, moreover, tended to recur more rapidly after periods of rest than is usual in disc cases. Radiological examination disclosed a characteristic loss of definition at the affected interspace. One of the patients was operated on deliberately a year ago because of exacerbation of root pain and a gross bulging of the lumbosacral annulus was found distorting the first sacral root. The annulus was incised and about 10 c.c. of characteristic watery tuberculous pus and débris was evacuated by sucker. The pus contained the bacillus of tuberculosis. Root pain ceased promptly. Healing of the lesion was proceeding satisfactorily under treatment in a plaster shell until the patient's sudden and unexpected death from pulmonary embolus about nine months after the surgical interference.

*Tumour* in the vicinity of the cauda equina may cause lumbar backache and mono-radicular referred pain. One common tumour in this region is neurinoma growing from a nerve-root in the cauda equina. The tumour may not attract attention clinically until it has acquired sufficient size to fill the theca, and then can be likened to the piston of a syringe, being displaced caudally by momentary rises of intrathecal fluid pressure. It is not surprising that those patients often live in dread of the agony caused by sneezing, coughing, and defæcation. The history in those cases of root tumour is generally progressive and continuous; little benefit is derived from rest in bed. Lumbar puncture with manometry of course removes all doubt in such cases.

Another syndrome simulating tumour implicating the cauda equina is seen when there is a *massive protrusion of a lumbar disc*. We wish to devote special attention to this type of case because of the extreme importance of early recognition and treatment. There is a history of fluctuating symptoms typical of prolapsed lumbar disc, with a sudden exacerbation leading rapidly to compression of the cauda equina. Tumour compression does not behave in this manner. A few cases have resulted from manipulation under anæsthesia. The first recorded case in the literature, given by Goldthwait in 1911, was of this type.\* The paraplegia following manipulation was correctly ascribed to prolapse of a lumbar disc and was relieved without delay by laminectomy. Trauma is not necessarily a precipitating factor. We have seen recently a patient in whom the cauda compression syndrome developed suddenly while he was walking along a street.

\* Middleton and Teacher's case (also 1911) was at a higher level and caused compression of the spinal cord.

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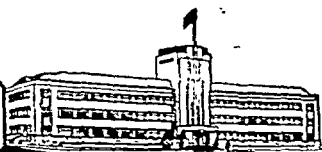


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The sensory roots in the cauda equina never regenerate if damaged, because the ganglia lie distally, at the intervertebral foramina. The sensory loss is apt to be permanent and has serious implications in respect of loss of control of the bladder and bowels. Any threat to the integrity of the cauda equina must be regarded seriously and must be relieved promptly by operation.

### TREATMENT

Relief of symptoms by rest is a feature of the disc syndrome, and a proportion of cases respond completely with no other measure. Immobilisation in plaster, radiant heat, short-wave therapy, and graded exercises after a period of recumbency, are the main lines on which conservative treatment is conducted. We find it difficult to form an accurate opinion of the general effectiveness of conservative treatment. Obviously the majority of our cases are selected. For many reasons it is not at present practicable to arrange a complete follow-up of cases, in all clinics, and perhaps those who carry out conservative treatment may quite understandably have an optimistic bias in assessing their results. We see and operate on the failures and we feel sure there is a risk that we may be biased in the opposite direction.

We do not advise operation in every case seen. About one patient in eight has so far recovered by the time he is seen by us that operation is not indicated. Some of those return later, but may have enjoyed up to several years of complete or relative comfort in the interval. In advising treatment the economic factor cannot be ignored. Conservative treatment involves a considerable loss of working time, with no guarantee against recurrence at the conclusion. In this connection the occupation of the patient has some bearing on the decision.

The operation is conducted through a median lumbar incision, exposing two or three lumbar spinous processes and laminæ on one or both sides at the required level. The ligamentum flavum is excised and the opening into the epidural space is enlarged with gouge and mallet, and with sphenoidal punches. The root is usually found displaced backwards and either medially or laterally; it is retracted medially as a rule with a root-retractor (J. G. Love) and the bulging pearly white or pale yellow disc comes into view. A circular incision through the annulus at the base of the protrusion affords entry into the disc and the contents are cleared out thoroughly with crocodile forceps of a pattern used in urological work. The cartilaginous plate is sheared off the vertebral bodies with a dental chisel. We are not satisfied until nothing but the annulus remains and we pay particular attention to the contralateral posterior corner of the disc if the approach be unilateral. Remnants of nucleus pulposus occasionally become

hydropic and swell up, and can cause a recurrence of symptoms. We have had five such recurrences—a recurrence-rate of just under 1 per cent. for the whole series—mostly in early cases before the need for thorough clearance of the disc was appreciated. Hæmostasis in the wound, especially in the deeper layers, must be perfect before closure.\* The commonest operative finding is an encapsulated eruption of nucleus pulposus through a rent in the annulus fibrosus. The annulus in other frequent cases has not ruptured but has yielded diffusely in its lateral part. In several cases the nucleus pulposus has been extruded and has been found lying free in the epidural space, sometimes at a distance from the aperture in the annulus. There is reason to believe that some of our earlier "negative explorations" may have been cases of this type and we now make it a practice to remove the half-lamina if the discs at first seem normal. The extruded nucleus pulposus may lie completely hidden under a lamina and could easily be missed without hemilaminectomy.

Exercises are commenced in bed on the sixth day after operation. The patient gets up on the tenth day and is put through a course of graded exercises supplemented by games and occupational therapy which restore mobility of the back. Finally he engages in physical training under a trained instructor.

Male patients on the average are fit to resume work not involving backstrain about eight weeks after operation, and as a routine heavy work is interdicted for three months. It is made plain to the patient that thereafter he can undertake the heaviest work without any qualms. Females tend to convalesce more rapidly than males, and this may perhaps be ascribed to the rather easier operative access in the female.

Our series of lumbar disc cases to date comprises 540 cases. The age incidence has been mainly in the three decades from twenty to fifty years, and of course a fair proportion of the cases have been drawn from the several Services. Among the civilians 70 per cent. were males, 30 per cent. females.

With regard to trauma as a precipitating factor, 60 per cent. gave a history of sudden trauma, 20 per cent. were exposed to habitual backstrain, and in 20 per cent. the symptoms had developed spontaneously. Concerning the level affected, 65 per cent. of the protrusions occurred at the lumbosacral disc; L. 4-5 disc was concerned in the remainder. There were only two cases with a syndrome referable to the L. 3-4 disc, confirmed at operation.

Right and left side were affected with equal frequency; the rupture was bilateral in 10 per cent.

Multiple disc protrusions occur, and merit comment in passing. More than one protrusion has been encountered in 14 per cent. of the series, including the 10 per cent. with bilateral protrusion of one disc.

\* Silk is used throughout in closure. The muscles are approximated to interspinous ligaments with mattress sutures which take only a shallow bite of muscle on each side.

In one case five protrusions were suspected clinically and found at operation, and two other cases yielded a crop of four protrusions. The existence of a bilateral protrusion can be suspected if there is a history of alternating sciatica—one side flaring up then dying down, followed perhaps by an interval of normality before the opposite side gives trouble. If the symptoms are bilateral concurrently, one side usually being consistently the worse-affected, a paramedian rupture is the usual finding at operation. A case presenting symptoms predominantly referable to one nerve root and clinical signs predominantly referable to a neighbouring root on the same side should be suspected of having two prolapsed intervertebral discs at adjacent interspaces.

A series of 235 civilian and military cases, operated on from January 1942 to December 1944, had been followed up. Of these 90 per cent. returned to their previous activities; in 10 per cent. the subsequent occupation required modification on account of residual disability. This latter group comprised 22 patients; residual disability was attributable to operative infection in 45 per cent. of those, to neurosis in 40 per cent., and to some unrelated medical condition in 10 per cent.

Two operative deaths have occurred in the series. Both were cardiac deaths, under cyclopropane anaesthesia.

### CERVICAL DISCS

The cervical discs are much less commonly affected than those in the lumbar region. The respective syndromes have otherwise much in common; in both, the discs at the lower end of the segment of the vertebral column are those almost exclusively affected; the history is one of spinal discomfort associated with referred root pain. In both the grosser protrusions compress the contents of the theca—cord in the cervical region and cauda equina in the lumbar region. Thus many cases masquerade initially as cervical spinal tumours. The mechanism of injury sometimes described by patients with prolapsed cervical discs is noteworthy and takes the form of a sudden alteration of the position of the body, as by a push or by sudden shift of a load that is being carried, at a time when the muscles of the neck are not "on guard." The inertia of the head causes a sudden lateral flexion or other movement of the neck. A significant proportion of the cases have dated their disability from an episode of this type.

The description of the clinical features can best be illustrated by recounting the story of Driver H., a case typical of the root compression syndrome.

This soldier, aged 40 years, had spontaneous onset of pain in the lower part of the neck four months previously. The pain was felt posteriorly and to the left of the midline. In a few days it radiated to the upper part of the left scapula, then down the back and outer side of the upper arm and

along the outer border of the left forearm. This extension of pain occurred in stages spread over a period of about ten days; by then the discomfort in the neck had eased off and numbness now appeared in the left index and distal part of middle finger. There were no paræsthesiæ or "pins-and-needles" in this case, though that is a common symptom. The position of maximum ease was supine, with arm bent up and the hand underneath the head. Pain was referred deeply under the left clavicle on coughing, and pain in the upper limb was aggravated by rotation of the head to the affected side. Pain disappeared gradually over many weeks from the proximal half of the affected limb, but the numbness of index and middle fingers persisted.

Examination of the neck showed nothing abnormal apart from some limitation of rotation to the affected side. Pressure on the vertex, and stretching of the brachial plexus by lateral flexion of the neck away from the affected side together with downward tension on the upper limb, both exaggerated the referred root pain. The left supra-spinatus muscle fasciculated, and there was weakness of the grip and of dorsiflexion of the wrist. The triceps reflex, and power in the muscle, were depressed. Cutaneous sensory depression involved the index and middle fingers and a short strip up the middle of the dorsum of the hand. Proprioception was normal. Lumbar manometry was normal and so also was the analysis of the lumbar cerebrospinal fluid. X-rays showed a markedly narrowed space at C. 6-7.

The expected compression of the seventh cervical root was found at operation and was relieved.

Those cases in which the sixth cervical root is involved show some weakness and wasting of biceps and brachioradialis, with depression of the biceps reflex. Extension of the wrist has usually been weakened somewhat. The sensory depression has been on the pre-axial border of the forearm and hand; in some cases the sensory loss has been limited to thumb, index, and thenar eminence.

Those patients who exhibit a cord-compression syndrome generally give a history of pain in the lower part of the neck coupled with a so-called "brachial neuritis" preceding the onset of the disabilities referable to the spinal cord. Those early symptoms may be mild and evanescent, and so may not be volunteered in the patient's account of symptoms. In general the syndrome has no other features distinguishing it from that of spinal tumour. We have seen a few cases with a bizarre picture; one is in the ward at present, whose dominating symptoms were unilateral and progressive pain and paræsthesiæ in trunk and limbs, suggesting rather a thalamic lesion.

In other cases the existence of a pathological disc is brought to light by accidental trauma.

A middle-aged farm worker was thrown from his pedal cycle and struck his head on the grass verge as he landed. There was immediate quadriplegia and anæsthesia from the arms downward. Radiological examination showed no fracture or dislocation but several of the intervertebral spaces were pathologically narrow and there was "lipping" of many of the vertebral bodies. Lumbar manometry showed a complete spinal subarachnoid fluid block. The cerebrospinal fluid was not blood-stained. At operation three

old fibrosed and ossified protruding discs were found to have encroached upon the vertebral canal sufficiently to compromise the cord and rendered it unable to withstand the acute flexion injury without contusion.

The series consists of twelve cases. The picture was exclusively that of cervical radiculitis in eight, affecting the sixth cervical root in three cases and the seventh root in the remaining five. Among the four cases with a cord-compression syndrome the C. 3-4 disc was pathological in two patients, and in one of these the disc at C. 6-7 was also prolapsed. The interspace at the affected level in the cervical region is always narrowed conspicuously and this is easily discerned radiologically, particularly in lateral view. In antero-posterior views the interspace is uniformly narrowed and in conformity with this one finds cervical protrusions to be either bilateral or to consist of a prominent transverse fibro-osseous ridge extending across the anterior wall of the vertebral canal. We have latterly always explored at the affected level on both sides, even though, as usual, symptoms have been unilateral, and so far have always found the disc to be prolapsed bilaterally and almost symmetrically.

The lumbar cerebrospinal fluid has been normal in all cases, except in those with compression of the spinal cord. In this latter group there was a partial spinal blockage on jugular compression in all but one of the four cases with a cord-compression syndrome.

The operation for decompression of a cervical root consists of cutting a window in the dorso-lateral wall of the vertebral canal, removing adjacent margins of laminae with gouge and mallet and with a small sphenoidal punch. We have come to the conclusion that forcible retraction of the cervical roots is to be avoided on account of the considerable post-operative root-pain induced thereby. Some retraction is unavoidable in order to expose the average prolapsed cervical disc because the root always overlies the protrusion.

Laminectomy is required in the cases with compression of the spinal cord. Experience with one case has led us to believe that the theca should be opened at operation and some of the attachments of the denticulate ligament should be divided. This permits a wider exposure of the epidural space and of the disc, and allows the cord to rotate slightly on its long axis as the theca is retracted medially.

Prolapsed intervertebral disc in the thoracic region causing neurological disturbance appears to be a rarity, and we shall do little more than mention that some individual cases have been reported, mostly brought to notice by reason of compression of the spinal cord. We have knowledge of a few cases of intercostal neuritis probably due to prolapsed thoracic intervertebral disc, but the symptoms were not sufficiently disabling or persistent to warrant exploration and so the lesion could not be confirmed.

In conclusion we think it right and proper to indicate that we act as spokesmen for the team of medical and nursing personnel whose efforts have

been applied towards the investigation and management of those several hundreds of patients. Mr Norman Dott is the captain of the team, and like all good captains inspires the energies of the players. At times we would even welcome a referee to blow his whistle and call a brief halt when there is a particularly heavy spate of patients with pathological discs.

It will be noted that we have made practically no reference to the rapidly growing literature, and have not mentioned the names of pioneers such as Schmorl, Barr and Mixter, or of those such as Spurling, Love, Pennybacker, O'Connell, and a host of others who are in the van of current thought on the subject. We have based this communication largely on the personal clinical experience of the team, considering that most of you would be interested chiefly in the practical problem of recognising the syndromes of prolapsed intervertebral disc.

### DISCUSSION

*Mr Smillie.*—It has been suggested that I should limit myself to indications for conservative treatment, a description of the method used, and my experience of the rehabilitation of industrial workers at Gleneagles. In the past six years 150 cases have been admitted to the Orthopædic Hospital at Larbert.

The indications for conservative treatment have been based upon the number and severity of attacks and on the occupation of the patient. We have selected for conservative treatment all patients in a first attack and cases with a history of one or two relatively mild attacks in the past. We have made no attempt to treat cases with very long histories or cases in the throes of a severe attack who gave a history of many severe attacks in the past. In those cases engaged in the heavy industries, such as coal mining and iron moulding, we have, when in doubt, tended towards the recommendation for operative action even though, as I will show later, there is some doubt, despite the brilliant results of operation, if cases are ever fit for the heaviest type of employment.

The treatment we have used is the most simple and the most common which is applied to any condition in medicine or surgery, namely, rest.

In disc lesions this can be obtained in two ways, rest in bed or local rest produced by the immobilisation provided by a plaster cast, but which permits the patient to remain ambulatory.

Most of the patients have been Service personnel who of necessity required to be hospitalised and for whom an adequate number of beds were always available. The first line of treatment has therefore been rest in bed.

Immobilisation in plaster was used in all cases which failed to react to three weeks' rest in bed, civilians for whom hospitalisation was not possible for domestic or economic reasons, V.I.Ps. who could not afford the time to rest, and certain cases with sedentary occupations.

The most common method of local immobilisation is a plaster cast of the same type as that used for fractures of the spine. While satisfactory for fractures of the spine, I do not consider that it provides sufficient immobilisation in disc lesions, and it provides no immobilisation at all of the hip. The method which we have used, in a total which now exceeds 50 cases, has been to reduce the lumbar scoliosis and reconstitute the curve and immobilise both spine and hip in the corrected position. This is carried out by giving the patient an anæsthetic and placing him on the pelvic rest of an orthopædic horse and permitting both legs to sag gently towards the floor. This reproduces

the lumbar curve and undoes the scoliosis. If the patient is middle-aged or over, or has had the scoliosis for a very long time, we are careful not to overdo the reduction. The affected limb is then raised to the mid position and placed directly below the pelvis and a close-fitting plaster case applied from about the level of the nipples to immediately above the knee. The effect of raising the affected limb while the other remains hyperextended is that the reduction of the lumbar deformity is maintained while the plaster immobilising the affected leg and lumbar spine is applied. This treatment gives immediate relief from pain in the leg in a very large proportion of cases. It is of course a somewhat rigid method of immobilisation, more so than an ordinary plaster jacket and is in itself irksome. Sitting in a chair other than on the very edge is impossible and meals must virtually be eaten off the mantelpiece; but most patients are only too glad to wear it for the arbitrary period of six weeks in view of the immediate relief of symptoms, and it is certainly of the utmost value to patients who shrink at the prospects of prolonged rest in bed or who for business or domestic reasons must remain ambulatory. I can also add that several patients, transferred from other hospitals, in whom an ordinary plaster jacket failed to give relief, were completely relieved of pain by this method.

In a certain number of cases we have made the symptoms very much worse. If the pain in the back or the leg is worse the next day we remove the plaster immediately. It is necessary, however, to differentiate between the discomfort of having the lumbar spine put into extension in plaster, and a genuine increase of previously existing symptoms.

I told you that most of our patients were Service personnel. I cannot therefore give you any statistics as to the ultimate fate of the patients we have treated conservatively. I know of course from my own experience that a number of them have relapsed even within a short time and I can only say that if they do relapse it is merely a further indication for operative action.

In regard to our experience of the rehabilitation of these cases at Gleneagles, 55 cases have passed through the Centre at an average age of 38. Twelve cases are at present in the Centre and I do not propose to refer to them. Of the 55, the diagnosis was made at Gleneagles for the first time in 44 cases. The labels under which they came into the centre were fibrositis, low back pain, pain in the hip or leg, or just sciatica. Of the 55, 32 cases were treated conservatively and 23 by operation. Sixteen of these latter cases were referred for operation from Gleneagles, having failed to improve by conservative means.

In following up the cases, it transpires that 13 cases returned to their former occupation. Of these 13, 12 had been treated conservatively, one by operation. Ten cases had returned to light work; 9 of these 10 have been treated conservatively, one by operation. Eight cases had been retrained in a new light occupation. Fourteen cases were unemployed and 10 cases have not been accounted for. Statistics over such a small number of cases means very little, but does tend to confirm an impression that despite the brilliant results in the relief of symptoms which follow operation in a large percentage of cases, the patients, usually because of low back pain, fail to return to the heaviest occupations. It should also be remembered that in the number to which I have referred, only the very worst cases of the longest standing were referred for operation.



*Dr J. K. Slater* expressed disbelief in the prevalence of the condition. Conception of sciatica has changed from being a radiculitis and neuritis to being due to the prolapsed nucleus pulposus, during the past twenty years, whereas in reality there are a large variety of causes of secondary sciatica. In the Mayo Clinic Henderson states that out of 5500 cases of back and leg pain 13 per cent. were positive prolapsed discs. This is a significant figure, but interpretation of the many smaller numbers published is difficult in view of the tendency to gravitate to special departments.

With regard to treatment, patients treated along conservative lines were relieved or cured within a month or two. After operation time of recovery is eight weeks to three months. Conservative treatment was advised first, but where there was excruciating pain or for occupational reasons operation was recommended.

*Mr W. V. Anderson* brought up the point that sciatic pain recurs with cold and damp. This might be due to increase of fluid in the blood and tissues due to the humidity of the atmosphere. These patients gave a typical disc history—a combination of fibrositis and low back pain. Fibrositic nodules, though present, may not be tender on pressure.

Mr Anderson, in referring to his work under the Ministry of Pensions, said they saw very few recurrences of symptoms. Those which did were possibly due to neurosis.

*Mr G. L. Alexander*, replying, said that he was glad Mr Stirling had mentioned the suspension method in conservative treatment of the prolapsed disc. There was no doubt that in some cases the disc-protrusion can thus be reduced and with the patient recumbent for a few weeks thereafter a cure may be effected.

Mr Alexander said he did not mention epidural injection because usually it failed. If it increased the pain at the time of injection it was thought by some to be diagnostic of a pathological disc, but general experience shows that this is not a reliable deduction. A lumbar epidural injection of novocaine followed by saline often plays a useful part in causing the pain of a radiculitis to subside more rapidly.

With regard to static arthritis, in many cases the intervertebral space becomes narrower after the centre of the disc has been removed. On the other hand, if this were a serious factor in the development of arthritis one would expect that a large proportion of operated cases would complain of backache after operation, and that had not been their experience so far. Such an eventuality attributable to static arthritis would certainly call for a fusion operation.

In connection with return to former occupation, Mr Alexander was of the opinion that many miners take the opportunity afforded by their disability of changing their occupation, usually to one in which they can enjoy fresh air and sunlight.

With regard to diagnostic criteria, Mr Alexander said that he had already mentioned reference of pain distally in the lower limb on pressure to one side of the spinous processes; for the rest it was a matter of assessing the available facts on the lines given in the paper. Differential diagnosis was sometimes difficult; in about 10 per cent. of cases one could not confidently assert that a pathological disc was the cause of symptoms.

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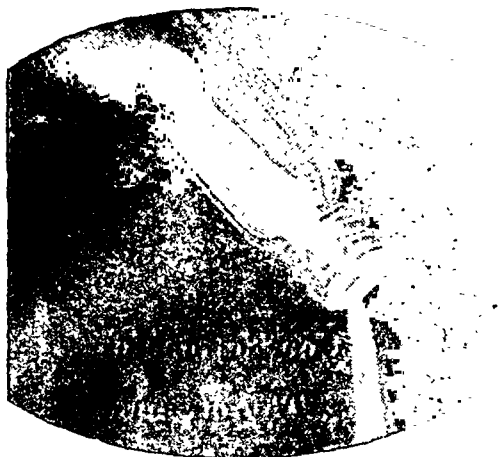
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Epidural injection to the amount of 300 c.c. is a large volume and would be responsible for rather severe headache. The capacity of the epidural space with lumbar needles *in situ*, permitting the theca to collapse, has been given as about 200 c.c. in papers on air myelography. There is sometimes temporary improvement after an epidural injection but usually the disc has to be removed later. It is postulated that adhesions are perhaps broken down by the epidural injection. Certainly fibrous adhesions of the roots to adjacent structures are quite often found at operation, and marked benefit accrues from division of those adhesions.

As to when a case should be referred to a neurosurgeon, Mr Alexander said that one must be guided by the recurrence of symptoms and the amount of disablement. It was evident during the war years particularly that symptoms referable to a pathological disc often resulted from a change of occupation, notably in those previously employed in sedentary work who had to embark on strenuous military training.

With regard to sciatica as a symptom, Mr Alexander said that his remarks were not intended to embrace "sciatica" in all its aspects; he had been alluding to referred sciatic pain of mono-radicular type and not to the wider reference of pain and sensory loss that is characteristic of affections of the sciatic nerve.

He was of the opinion that in some instances an unsatisfactory operative result was due to hæmatoma in the wound, and in others was attributable to a low-grade operative infection. There was no doubt that climatic changes affected patients with nerve lesions of various types, and the radiculitis due to ruptured disc was no exception.

Mr Alexander said that fibrositis was often to be found in cases of prolapsed disc but he was uncertain of its significance. The fibrous nodules seemed to bear no relation to the severity of symptoms and often persisted long after operative cure.

Mr Alexander mentioned four cases with primary lumbar backache but with no physical signs indicative of root-compression, yet at operation a pathological disc had been found in each case. Young people were more likely to have soft yielding protrusions; in old people the protrusion was often densely fibrosed and perhaps even ossified. Most cases in the elderly group responded to conservative treatment in some measure, but it was difficult at present to say for how long, and in what percentage a substantial amelioration was effected.

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# PNEUMOPERITONEUM IN THE TREATMENT OF PULMONARY TUBERCULOSIS

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## INTRODUCTION

THE use of pneumoperitoneum in the collapse therapy of pulmonary tuberculosis has now passed the experimental stage and reports which have appeared in both the British and American literature during the past few years show that this procedure is being used on a rapidly widening scale and in a great variety of cases. The first report of its employment in two cases by Vajda in 1933 was quickly followed by a comprehensive paper by Banyai (1934) who had utilised pneumoperitoneum in conjunction with phrenic paralysis. In 1938 the same author reported a series of 150 cases treated by pneumoperitoneum but he did not attempt to evaluate the results nor did he lay down any definite indications for the employment of the method. Sporadic reports subsequently appeared which indicated that the procedure was passing through its trial stages but it was not until 1941 that a comprehensive evaluation of its possibilities was attempted by Rilance and Warring and by Fowler who published results in a series of 55 and 56 cases respectively. In 1943 Clifford-Jones and MacDonald, working at Clare Hall Sanatorium, reported a series of 63 cases followed by Rudman (1943), Rilance and Warring (1944), Edwards and Logan (1945), Crow and Whelchel (1945), and Anderson and Winn (1945).

A survey of these papers published during and since 1941 gives a very fair picture of the evolution of the treatment. In the early stages most workers applied it only to advanced cases for whom no other form of therapy was available. The results, although unimpressive, were not wholly disappointing and provided encouragement for the further exploration of its possibilities on more promising clinical material. Its rôle in collapse therapy is now becoming more clearly defined and the later reports have attempted to indicate the type of case in which benefit may reasonably be expected. Thus Fowler recommends its employment in the following circumstances:—(1) advanced cases in which no other procedure is applicable, (2) cases of bilateral disease with adhesive pleuritis preventing artificial pneumothorax, (3) cases of unilateral disease, with adhesive pleuritis, too acute or too inadequately stabilised to permit of thoracoplasty, (4) cases showing predominantly basal lesions although even here pneumothorax should still be regarded as the method of choice, (5) cases in

which it is desired to enhance the effect of a paralysed diaphragm, (6) cases of uncontrollable hæmorrhage.

Rudman, and Crow and Whelchel have commented upon the value of pneumoperitoneum in preparing a poor surgical risk for a later thoracoplasty, a point stressed still further by Rilance and Warring who are also much impressed with the success of pneumoperitoneum in basal lesions. Edwards and Logan, in a thoughtful and detailed analysis of a series of 50 cases conclude that the type of lesion is of more importance than its actual situation in the lung field, pointing out that a successful result is unlikely in old-standing fibrotic disease and in adherent cavities, owing to the mechanical factors involved, even should an apparently adequate diaphragmatic elevation be secured. These same authors have recorded the complications which they encountered, the most notable being an almost universal loss in weight among those patients receiving refills. In 4 cases they had small peritoneal effusions and in 3 cases troublesome dysmenorrhœa. Rilance and Warring in their second paper reported a considerable increase in the incidence of acute appendicitis amongst patients receiving refills but were unable to suggest an acceptable explanation.

## RESULTS

Since the beginning of 1943 thirty-five cases have been treated by pneumoperitoneum in Tor-na-Dee Sanatorium and an attempt has now been made to assess results and to record some of the more interesting clinical problems involved. In presenting our results in this admittedly small series we have grouped them under two headings taking into account (1) the indications and (2) the extent of pulmonary tissue involved in the disease process. Results have been classified as successful, partially successful or failed and in assigning cases to their appropriate group we have considered only the immediate objective for which the pneumoperitoneum had been initiated. Thus in cases of bilateral disease in which the pneumoperitoneum had been designed to control the contralateral lung in preparation for thoracoplasty a successful result has been recorded when the case was sufficiently stabilised to proceed to major surgery. The objective in many of these cases was a limited one and we wish to avoid making any exaggerated claims for the form of therapy under review.

In Table I the two cases recorded as being "far advanced" represent our early excursions into the peritoneal cavity. The results of our efforts combined with a study of the achievements of other workers in similar cases convinced us that pneumoperitoneum was not a method to be recommended when all else had failed, and thereafter we endeavoured to apply it with more discrimination. It appeared logical to utilise it in supplementing an ineffective pneumothorax where adhesion section had been incomplete and where a concomitant phrenic paralysis had been insufficient to secure cavity closure. The

majority of our cases, however, represent patients in whom pneumothorax was either contra-indicated, for example, on account of acute exudative disease, or impossible, by reason of extensive pleural adhesions, and in a proportion of these the treatment was used only as a method of preparation for major surgery. In some of the last

TABLE I  
*Results Classified According to Indications*

	Supplementing Partially Effective A.P.	A.P. Contra-indicated or Impossible.			Far Advanced Disease.	Total.
		P.P. and Phrenic Paralysis as Sole Measure.	P.P. and Phrenic Paralysis in Preparation for Major Surgery.			
			Homolateral Lung.	Contralateral Lung.		
Successful . . .	3	6	3	4	0	16
Partially successful	0	2	2	1	0	5
Failed . . .	4	7	1	0	2	14
Total . . .	7	15	6	5	2	35

group the contralateral lung was the objective, in others our aim was to control a recent bronchogenic spread in the homolateral lung and on the whole we had reason to regard our results in both these pre-operative groups with moderate satisfaction.

TABLE II  
*Results Classified According to Extent of Pulmonary Involvement*

	All Zones.	Upper Zone.	Upper and Middle Zones.	Middle Zone.	Middle and Lower Zones.	Lower Zone.	Total.
Successful . . .	2	2	2	3	2	5	16
Partially successful .	1	1	1	1	1	0	5
Failed . . .	3	4	2	2	3	0	14
Total . . .	6	7	5	6	6	5	35

In Table II we have endeavoured to re-group our results according to the situation and extent of the pulmonary involvement and here the most striking fact is the uniformly successful outcome of treatment in those lesions confined to the lower zone. This is in accord with the views of Rilance and Warring and of Fowler.

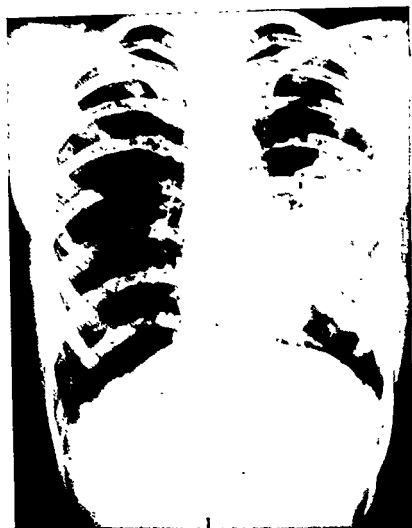


FIG. 1.

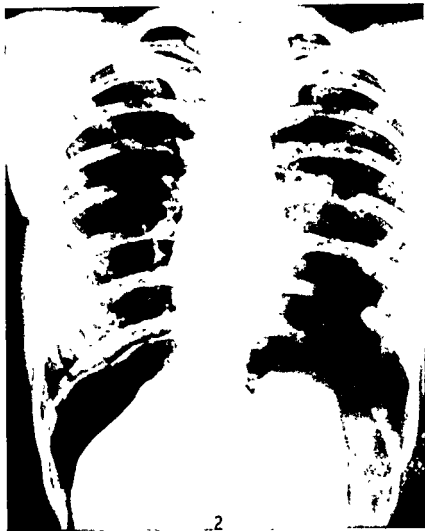


FIG. 2.

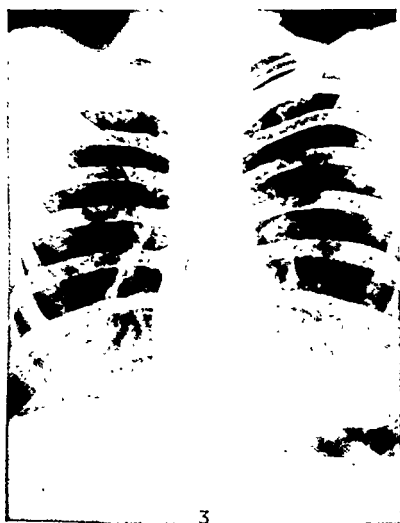


FIG. 3.

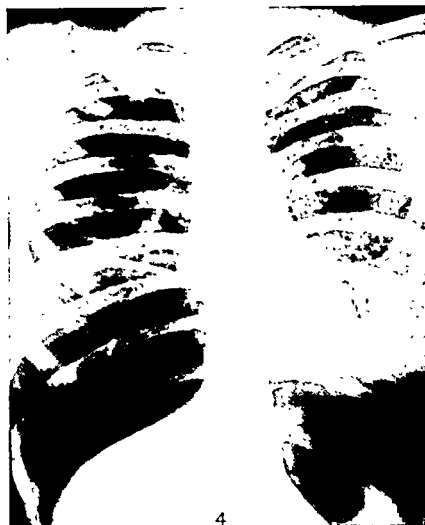


FIG. 4.



FIG. 5.



FIG. 6.





FIG. 7.

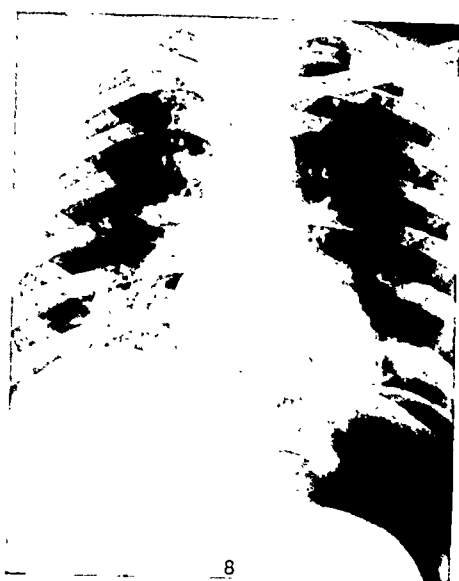


FIG. 8.

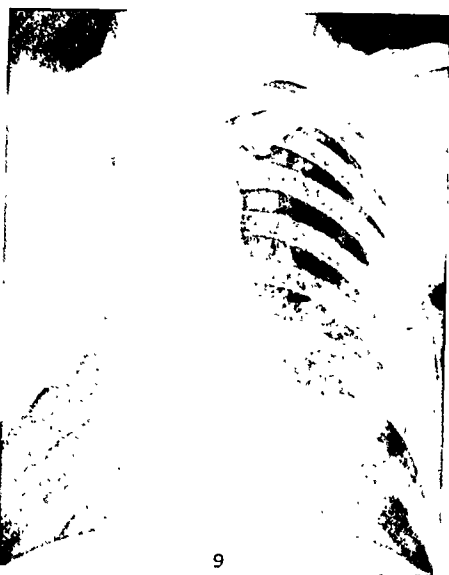


FIG. 9.



FIG. 10.

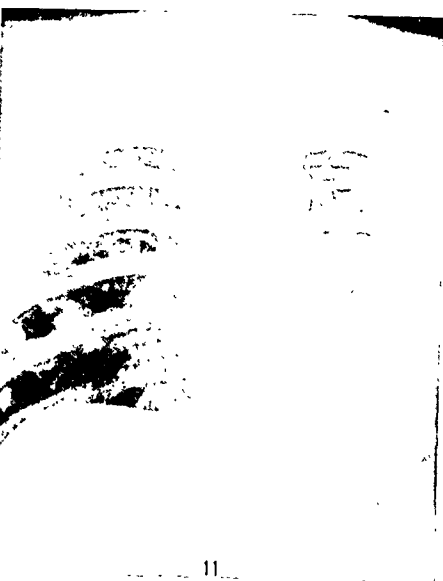


FIG. 11.



FIG. 12.

Protagonists of pneumoperitoneum have claimed for it a relative freedom from complications and from the evidence to date it does appear to lack many of the undesirable sequelæ which may intervene during the course of pneumothorax. In our cases complications were few. In one instance refills had to be abandoned at an early stage owing to signs of cardiac embarrassment. Here the patient already had an artificial pneumothorax and in addition the opposite lung was fairly extensively diseased. Cessation of refills relieved the situation within a few days. We had one case of mild mediastinal emphysema and another case in which the bowel was accidentally perforated during a refill, leading to the passage of a large volume of flatus: further refills in this case proceeded without interruption. In two instances the liver and diaphragm were found to be firmly adherent *ab initio* and we failed completely to secure any elevation of the diaphragm. In two other cases a good diaphragmatic rise was obtained but during the course of treatment adhesion formation occurred between the diaphragm and the upper surface of the liver when the refill interval was unduly extended and the subdiaphragmatic air space obliterated. We had two cases of acute appendicitis requiring immediate operation thus confirming the suggestion by Rilance and Warring that this condition may have to be regarded as a complication of pneumoperitoneum. No cases of peritoneal effusion were encountered nor have we been able to confirm the finding of Edwards and Logan that patients receiving pneumoperitoneum show a steady fall in weight.

### TECHNIQUE

We have little to add to the accepted technique of pneumoperitoneum. The treatment should be initiated a few days after phrenic paralysis and, while local anæsthesia is desirable on the first occasion when a stout, short-bevelled needle should be used, we have not found it necessary for subsequent refills which may be given with sharper and finer needles. The site of choice is slightly above and to the left of the umbilicus. Perforation of the bowel is rare and is less likely to give rise to complications than is the introduction of air into the abdominal wall. In the latter event an unduly sharp rise in manometric pressure is noted after the introduction of only a small quantity of air. It is our practice to give 700 c.c. of air at the initial injection and from 800 to 1000 c.c. at each refill. Refills are spaced according to the X-ray appearances and the progress of the lesion, and they are seldom required at shorter than weekly intervals after the first fortnight.

### ILLUSTRATIVE CASE REPORTS

CASE I.—Girl, aged 19. Acute exudative lesion involving lower half of left lung. Sputum positive. Febrile. Disease considered too acute for pneumothorax (Fig. 1). After nine months' treatment by phrenic paralysis and pneumoperitoneum patient was afebrile and sputum negative. Fig. 2 shows clearing of former infiltration with contraction of lower lobe.

CASE II.—Woman, aged 25. Small cavity in right upper zone (Fig. 3). Sputum positive. Afebrile. Right A.P. failed. Fig. 4 shows cavity closure after nine months' treatment by phrenic paralysis and pneumoperitoneum. Patient sputum-free.

CASE III.—Man, aged 22. History of pulmonary tuberculosis at age of fifteen with subsequent relapse and cavity formation in left lower and mid zones (Fig. 5). Left A.P. failed and major surgery contra-indicated on account of site of lesion and instability of contralateral lung. Sputum positive. Phrenic paralysis and pneumoperitoneum completely failed to influence disease (Fig. 6).

CASE IV.—Man, aged 26. Infiltrative lesion right mid and lower zones. Sputum positive. Afebrile. Right A.P. failed. Following phrenic paralysis pneumoperitoneum was attempted. Upper surface of liver adherent to diaphragm on posterior aspect (Fig. 7). No further elevation of paralysed diaphragm obtained (Fig. 8). Pneumoperitoneum abandoned.

CASE V.—Man, aged 34. Following right upper thoracoplasty developed very acute spread of disease to left base with rapid cavitation (Fig. 9). A.P. and phrenic paralysis contra-indicated owing to doubtful cardiac reserve. Pneumoperitoneum initiated and maintained for six months producing considerable cavity contraction (Fig. 10).

CASE VI.—Man, aged 27. Eighteen months after successful L.A.P. developed small infiltrative lesion in right lower zone (Fig. 11). Sputum positive. R.A.P. undesirable owing to limited extent and situation of lesion. After six months' treatment by phrenic paralysis and pneumoperitoneum Fig. 12 shows lesion completely controlled. Sputum negative.

## DISCUSSION

In reviewing such a limited series of cases the temptation to draw conclusions must be resisted and we propose to confine our discussion to recording some of the impressions which we have formed, impressions which will, we hope, be confirmed by time and experience. In our entire series pneumoperitoneum was only used on one occasion without an accompanying phrenic paralysis and although on that occasion a totally unexpected success was achieved we do not feel that pneumoperitoneum *per se* is likely as a rule to produce any appreciable effect on a pulmonary lesion. It should be combined with phrenic paralysis and the indications for the two procedures must, therefore, be regarded as essentially the same. We have been impressed with its value in the five cases in which we used it to control disease in the contralateral lung preparatory to thoracoplasty. We chose it in these cases because we felt that the type of disease was such that with pneumothorax the risks of pleural effusion would have been considerable and this complication would have seriously interfered with our plans for surgery. In no instance had we any reason to be dissatisfied with our choice.

Where pneumoperitoneum and phrenic paralysis were used as a single procedure to control a specific lesion the most notable successes attended those cases in which the disease was confined to the lower zone, but a proportion of successes in other areas indicates that the procedure need not necessarily be exclusively confined to the treatment

of basal disease. For instance, in one case a small cavity at the extreme apex responded most satisfactorily and closure was confirmed by tomography three months after the commencement of the treatment. Eighteen months after the conclusion of treatment in this case a small fibrous nodule was all that remained of the original lesion. As a means of controlling acute exudative disease in which the possible complications of pneumothorax are a deterrent pneumoperitoneum appears to have a definite place and it can, if necessary, be replaced by a pneumothorax or by a thoracoplasty at a later date.

We find ourselves unable to lay down any rigid rules for the duration of pneumoperitoneum. In our cases it has varied from the six months considered necessary to prepare a mildly involved contralateral lung for thoracoplasty to one case in which refills have been continued for over two years. There is no reason why a successful pneumoperitoneum should not be regarded in the same light as a pneumothorax and refills maintained until all doubts concerning pulmonary healing have been eliminated. It is claimed that pneumoperitoneum is a readily reversible procedure and that, unlike pneumothorax, refills can be allowed to lapse and be resumed again at a later date if necessary. We have found this to be so in some of our cases but the formation of hepato-diaphragmatic adhesions in two instances indicates that resumption of treatment will not always be possible.

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## SEQUELÆ OF TROPICAL DISEASE— SKIN CONDITIONS \*

By G. A. GRANT PETERKIN, F.R.C.P.Ed.

ON arriving abroad, most dermatologists were surprised to find that, instead of having to cope with strange and wonderful dermatoses, almost to the exclusion of everything else, the common kinds of skin disease were just as frequent in hot climates ; and that tropical diseases accounted for only a small fraction of their practice. But they also found that certain diseases which occurred at home were met with much more frequently and caused considerable disability.

I intend to mention only those conditions which may be encountered in practice here—in fact, since I came back to Edinburgh, I have seen one or more examples of the diseases which I will mention, with one exception—tropical ulcer.

### A. ULCERS

This is not the place to enter into a dissertation on “ Desert Sores ”—suffice it to say that this term covered many conditions—impetigo, ecthyma, diphtheritic and diphtheroid ulcers, etc. They had little to do with diet or hypovitaminosis but much to do with cross-infection, strong sunlight, lack of washing facilities, and minor injuries. The commonest ulcer seen was :—

(i) *Ecthyma*—exactly similar but often more severe than in Britain. The same factors were involved, an underlying disease such as scabies ; a lowered general resistance ; and poor skin hygiene.

(ii) *Diphtheritic Ulcers*—were only too common and were too often undiagnosed, sometimes with fatal results. The article by Cameron and Muir was one of the first written during this war to emphasise their importance, and it is noteworthy that a considerable number of cases have been seen in Southern England. In Africa and Italy the ulcers occurred most commonly in October and November, and appeared under different guises : (a) The usual type began as a *hard brawny swelling with lymphadenitis*, often considered to be a cellulitis. Within a few days the swelling disappeared and the typical ulcer was seen with a thick adherent black or yellow slough. When this separated, a very clean coral-red base was found with clear-cut edge, which was either circular or angular. (b) It might appear as a large *bulla* which ruptured, leaving the typical base, or as (c) *small ulcers*, especially over the dorsa of leg, hands, and feet, with no slough, but with the same clean bright-red base, and often diamond-shaped. Sometimes (d) deep *penetrating ulcers* in the webs

\* Read at a meeting of the Edinburgh Medico-Chirurgical Society on 6th March 1946.

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Fig. 1

### CASE HISTORY

The patient, aged 34, broke his leg while jumping between ships. A fracture involved the lower end of the left tibia and fibula. He was in plaster for about eight months and in Elastoplast for a further month or so. During these ten months he had numerous sequestra from the fracture site and when everything else had healed the ulcer remained at the inner side of the junction of the middle and lower thirds of the leg. On the 30th October he was admitted to hospital. The skin around the ulcer for at least 2" was found to be



Fig. 2

## Persistent Post-traumatic SKIN ULCERATION

### A cross leg flap graft and immobilisation with Gypsona

of poor quality. Radical excision of ulcer and surrounding area of unstable skin was performed. A cross-leg flap from opposite calf was sutured into the defect. The raw donor area was covered with thin razor graft, dressed with tulle gras (Jelonet). Previously applied Gypsona plaster boots were then joined with additional Gypsona bandages. After three weeks the plaster was removed and three days later the flap was divided. In two months the flap was completely healed and the patient discharged. The details and illustrations above are of an actual case. T. J. Smith & Nephew Ltd., manufacturers of Elastoplast, Jelonet and Gypsona publish this instance—typical of many in which their products have been used with success.



Fig. 3

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of the fingers or toes, often secondary to a fungus infection, were due to bacillus diphtheriæ, while it might complicate a septic skin condition such as impetigo, being only distinguishable by slow response to treatment and exuberant crusting.

Diagnosis depended on previous experience of the disease, and repeated bacteriological examination. Antidiphtheritic serum should be given in a large single dose, *e.g.* 48,000 to 96,000 units, depending on the lesion. Penicillin was helpful to a limited extent.

(iii) *Diphtheroid Ulcers*, seen occasionally in this country, were quite often encountered and were the ulcers most resistant to treatment. They were recognised by the pain, the filthy base, and the purple undermined irregular edge, and by careful bacteriological examination. The most effective treatment was excision of the ulcer, followed by wet dressings of  $\frac{1}{2}$  per cent. silver nitrate. Grafts merely became infected and broke down, while the action of penicillin was disappointing.

(iv) *Tropical Ulcers* fortunately heal readily when the patient is transferred from a hot damp climate and are not likely to be met with here.

(v) *Leishmaniasis Cutis*.—The incubation period of this disease varies from weeks to months or years, and so men who have been home for some time may develop this eruption while at home. For instance, in Italy, a number of men in the 6th Armoured Division developed these sores even eighteen months after they had left an area infested with sandflies. The lesions may be single or multiple, and cause no symptoms. Any part of the body may be affected but the exposed areas such as the face, hands and arms are usually involved. The condition is endemic in India, Iran, Iraq, Palestine, Syria, North Africa and Italy, and may closely resemble lupus vulgaris, even to the histological picture. One should suspect this disease in the presence of a chronic painless ulcer or boil-like swelling.

(vi) *Syphilitic* ulcers, especially ulcero-nodular syphilides, must always be suspected and a Wassermann taken.

## B. EFFECTS OF SUNLIGHT

(i) *Chronic Solar Dermatitis*.—Men who served in sunny climates tended to develop an actinic dermatitis, especially blond or red-haired people. It is characterised by atrophy of the skin with telangiectasia, pigmentation and keratoses, which tend to develop into carcinomata. Therefore one should suspect carcinoma in any patient who develops warty lesions on exposed areas such as the face or the back of the hands after serving abroad.

(ii) *Photosensitisation*.—Not a few men whose skins became light-sensitive abroad still react even to the attenuated sunlight in this "demi-Paradise." It will be found that most of these are cases of Sulphonamide Light Dermatitis. These eruptions usually closely resemble a severe seborrhœic eczema but can be distinguished by the



involvement of the lips, the neck, and the other areas exposed to light. Desensitisation is a slow and tricky matter.

### C. "PROFESSIONAL" DERMATITIS

In warm climates the excessive perspiration appeared to render the skin more liable to contact dermatitis, due to many causes—chemicals handled at work, such as Diesel oil; rubber contact dermatitis (respirators, physical training shoes, surgeon's gloves); textile dermatitis (due to khaki drill, woollen shirts, etc.), etc. Skins thus sensitised have tended to remain so on return to civil life, and bulk quite appreciably as a problem in industrial medicine.

### D. FUNGUS INFECTIONS

Were, of course, very prevalent overseas, and many men are still plagued with these, and what is more, have spread the disease, chiefly through baths and athletic clubs, to other members of the community. Any part of the skin is liable to be infected, but the ringworm commonly attacks the feet, hands, groins and axillæ. When the hands are involved, the disease may take the form of an "eczematoid ringworm" and may be mistaken for an industrial dermatitis, as fungus infections can assume protean forms, *e.g.* vesicular, squamous or keratotic lesions may be found. It usually shows first as maceration or desquamation between the fourth and fifth toes, may spread behind and between all the toes, on to the dorsum or sole of the foot, or may suddenly appear as a vesicular or vesicosquamous eruption on the instep or palms. The straightforward ringworm infections of the thighs and axillæ respond readily as a rule to fungicides, but it must be remembered that acute tinea of the feet and hands must be treated with soothing applications just like an acute eczematous outbreak.

### E. WARTS

Tended to be spread by the communal army life, plantar warts by the shower-baths, and condylomata acuminata by promiscuous sexual intercourse. These cauliflower-like warts flourished greatly in warm climates in the perianal region and the preputial sac, and many men have returned home to spread the infection. Fortunately, the older treatments have been superseded by the introduction of podophyllin resin, which is used in a strength of 12·5 or 25 per cent. in liquid paraffin or a cream base. It is applied thoroughly to the warts, left on for eight to ten hours and then washed off.

### F. LEPROSY

May possibly be encountered in men returning from the Far East. The macular patches may readily be mistaken for ringworm. Points to be remembered in the diagnosis are the presence of anæsthetic patches, thickening of the ulnar nerves, and nodules on the brows or lobes of the ears.

## G. TROPICAL LICHENOID DERMATITIS

Is a generalised dermatosis which has made its appearance in tropical and sub-tropical countries. During the first phase it tends to be pleomorphic, usually commencing on the feet or hands as a keratosis, and gradually spreading all over the body chiefly as purplish red blotches. In its final stage it closely resembles a hypertrophic lichen planus, even to the lesions in the mouth. It tends to persist



Tropical lichenoid dermatitis showing plaques with characteristic distribution.  
(Courtesy of Capt. J. Savage, R.A.M.C.)

for weeks or months, gradually resolving without any specific treatment. A leading article on this condition will be found in the *Lancet* of 1st December 1945. A major factor in the etiology is the ingestion of mepacrine as a malarial suppressive. Cases have been reported from most malarial areas—the Pacific, Australia, India, Africa and Italy. I have seen about 50 cases in Africa and Italy, and have observed 3 since returning to Scotland. The incidence per 1000 troops taking mepacrine is small, but this condition should be suspected in a man returning from a malarial climate with a widespread peculiar rash perhaps resembling lichen planus.

## SEQUELÆ OF TROPICAL DISEASE \*

By J. D. S. CAMERON, C.B.E., M.D., F.R.C.P.Ed.

Assistant Physician, Royal Infirmary, Edinburgh

### MALARIA

IN considering the medical sequelæ of tropical diseases the thoughts of most turn first to malaria. Let mine turn there too for a very important and perhaps very different reason—to emphasise that malaria *is not* to be a problem despite popular belief. A very large number have been infected with malaria parasites, yet the proportion who will show malaria on return will be comparatively small, and they will be easily handled, that is if we are ready in our diagnosis.

For practical purposes we need consider only two types of malaria, B.T. and M.T. The former is the malaria of relapses and the type likely to recur on return to Britain. Most of the M.T. will have been cured by the suppressive mepacrine treatment adopted in most theatres of war, for it has been amply demonstrated that such therapy when given daily is sufficient to destroy the M.T. parasites. With B.T. this is not the case. The daily administration of 0.1 g. of mepacrine is sufficient to ward off the attack of B.T. malaria, but relapse is possible after cessation of the suppressive regime. But all malaria burns itself out in about two years, and it was with this in mind plus the knowledge of the great success of suppressive therapy, that I made the opening statement that malaria would not be a problem.

In India and its adjacent theatres we adopted eventually an all-mepacrine (atebrine) treatment for malaria, giving the patient 0.9 g. on the first day, 0.6 g. on the second, and 0.3 g. daily for the succeeding five days. Thereafter the patient returned to the suppressive dose of 0.1 g. daily and continued with this. This treatment was aimed, not at the cure of the condition, but at the cure of the attack, followed by the return of the man to the fighting line and his continuance there. To keep the man in the line was the first task of a medical service in war, and in a theatre where man-power was so short, the fighting line so long, and the malaria mosquitoes everywhere, such a policy was more than ever necessary. We knew mepacrine had only a schizontocidal action and had little or no value as a gametocide, and that pamaquin (plasmaquin) had the reverse action with a low schizontocidal and high gametocidal effect. But we also knew that pamaquin treatment increased the stay in hospital, broke the mepacrine control of suppressive therapy, and further, that despite it the relapse rate continued high. The adoption of this policy justified itself by results, suppression was preferred to treatment, and consequently the

\* Read at a meeting of the Edinburgh Medico-Chirurgical Society on 6th March 1946.

number of cases of malaria fell to an almost unbelievably low level. The policy succeeded in India and Burma, but it may well be it will increase the number of cases among those repatriated. Even then the policy is simple—the disease must now be treated, and with a suitable combined therapy of quinine and/or mepacrine along with plasmoquin a ready response should be obtained.

If relapses occur, concurrent treatment with quinine and pamaquin for ten, or better, twenty-one days, is reported to give good results. This report comes from workers in England and on the Continent; our results in India were not equally good. Also from home come reports of good results with paludrine. This drug also has been shown to be non-toxic when combined with plasmoquin, and it would appear that a good second line of treatment is available. Yet a third alternative is available where frequent relapse is occurring—follow up the curative course of treatment with suppressive therapy, giving the patient 0.1 g. of mepacrine per day for the succeeding six months or one year. During that time it is highly probable that the malaria will become extinguished. The yellow coloration imparted to the skin may be a disadvantage but the male at least will prefer this to relapsing malaria.

Table I summarises the treatments available for malaria.

TABLE I

*Treatment of Malaria*

A. Combined treatment with quinine, mepacrine and pamaquin.

Days 1 to 3. Quinine 10 grains t.i.d.  
Days 4 to 8. Mepacrine 0.1 gramme t.i.d.  
Days 11 to 15. Pamaquin 0.01 gramme t.i.d.

B. Mepacrine and pamaquin treatment.

Day 1. Mepacrine 0.3 gramme t.i.d.  
Day 2. Mepacrine 0.2 gramme t.i.d.  
Days 3 to 7. Mepacrine 0.1 gramme t.i.d.  
Days 10 to 14. Pamaquin 0.01 gramme t.i.d.

C. Q10 P10 treatment.

Quinine 10 grains t.i.d.  
Pamaquin 0.01 gramme t.i.d. } Concurrently for 10 days.

This has also been employed as a 21-day course.

D. Combined treatment with paludrine and pamaquin.

Paludrine 0.025 gramme t.i.d.  
(i.e. 1 tablet)  
Pamaquin 0.01 gramme t.i.d. } Concurrently for 10 days.

Where relapses are frequent suppressive mepacrine may be used, following any of the above courses, giving 0.1 gramme mepacrine daily.

DYSENTERY

My opening remark about malaria applies even more to bacillary dysentery. The great success of the sulpha group of drugs, notably sulphaguanidine and succinyl sulphathiazole has wrought a wonderful

change in the outlook on this disease. Bacillary dysentery presents no problem.

In contrast, *amœbiasis* raises the greatest problem we face following tropical warfare. Cases of both intestinal and hepatic amœbiasis will be occurring in large numbers. In some parts of the Far East theatre where very large numbers of British troops were serving the carrier rate reached towards 40 per cent. A 20-25 per cent. infestation was a common finding. The incidence of the disease was proportionately high. In 1944 the number evacuated home from India as unfit for further service was 543. Faced with this menace India was vigorous in research in this disease. Two fully equipped research teams tackled the problem and interesting results will be available for publication shortly. Most of that work does not come within the scope of this paper, what does, however, will be referred to at the appropriate stage.

The sequelæ of amœbic infection to be expected in Britain are chronic intestinal amœbiasis and hepatic amœbiasis. The intestinal type may show in three ways: (1) Chronic recurrent attacks of dysentery, (2) chronic dyspepsia, (3) granulomata. It cannot be too strongly emphasised that for the diagnosis of intestinal amœbiasis there are two essentials:—

(a) The examination of a "hot" stool.

(b) The routine use of the sigmoidoscope, or less desirable, the proctoscope.

Too often the stool examination is carried out on a "recently passed" stool. Even in the heat of India this was found unsatisfactory. Either the patient must go to the laboratory or the microscope must go to the patient. The stool must be examined immediately it is passed.

In all military hospitals in India a commode was provided adjacent to the pathology laboratory and, if at all possible, the suspected dysentery patient went there to pass his stool. This procedure greatly increased the number of positive diagnoses. Sigmoidoscopic examination proved equally valuable. The rectum or lower large intestine showed characteristic ulcers in a high proportion of cases, the swab taken from these ulcers frequently yielded vegetative forms when none were obtained in the stool. Sigmoidoscopic examination was valuable in the early stage as a diagnostic procedure when the stools failed to yield amœbæ; after treatment it was equally valuable in prognosis, demonstrating if full recovery of the ulcers had taken place. Where this had not occurred further treatment and observation were imperative.

The longer diagnosis is deferred the less likely is the occurrence of cure. Our high incidence of relapses in India in the early days was not so much due to faulty treatment as to delayed diagnosis. Both clinician and pathologist must strive to fix the diagnosis at the first attack, and so allow treatment to be thorough before the condition becomes firmly established. One finding of our research team was

that 40 per cent. of cases present with a stool showing "dysentery exudate" which was previously regarded as all but diagnostic of bacillary dysentery.

A careful abdominal examination is necessary with special reference to the cæcum and descending colon. A large cæcum, with or without thickening, and a thickened and spastic descending colon are highly suggestive. As Mr Bruce has indicated, be careful, in those returned from the East, in your diagnosis of appendicitis, and of carcinoma of cæcum or rectum. It is in the two latter areas that granulomata are most frequent. By rectal examination the softer consistence of the amœboma may help. The therapeutic test by six injections of emetine incurs no great waste of surgical time, and will frequently produce a rapid reduction of a rectal "cancer."

Hepatic amœbiasis is the personal dread of all who have served out East. We have probably all been fortunate to escape intestinal amœbiasis, yet that but increases the dread, for the majority of cases of hepatic amœbiasis give no history of amœbic dysentery. This fact must be impressed, as reliance on a history of amœbic infection will result in many cases of hepatic abscess being missed. Suspect it in all cases of men returned from the East with pain in the upper right abdomen and lower chest, in all such with enlargement of the liver, and in all cases of unexplained signs at the base of the right lung. In such cases a right basal pleural effusion is commonly the first finding.

A careful examination of the liver is called for. Look for enlargement below the costal margin, but even more important, look for upward enlargement showing by diminished movement over the right chest and upper displacement of liver dullness. Then test for tenderness by careful palpation with one finger in the lower interspaces of the right side, especially the 8th to 10th interspaces in the axillary region. Follow up by compression of both sides of the chest laterally, and by the careful application of pressure over the lower part of the front of the chest. I have found another test useful—simultaneous deep pressure with the index fingers in the fossæ between the heads of the two sterno mastoids. If there is increased tension on the liver capsule there will be complaint of pain on this palpation of the right side. Similarly pain referred to the right shoulder region may be a valuable pointer to diagnosis.

Radiology should always be employed for the diagnosis of hepatic abscess, the screen examination being especially helpful. Immobility of the right leaf of the diaphragm, heightening and local bulging of the right leaf, and a small effusion in the right costophrenic angle, are the commonest findings (Cameron and Lawler, 1943).

It cannot be overemphasised that the treatment for all forms of amœbiasis is medical. The days of surgical drainage of hepatic abscess have gone. If drainage of an abscess is necessary it should be carried out by medical aspiration. Surgical interference is only called for when the abscess continues to enlarge despite repeated

aspiration and thorough treatment with emetine, or where mixed infection occurs. In the latter event the success of penicillin may even have made this a non-surgical condition. (Hunt, 1945).

No drug has been completely successful as an amœbicide when used alone. The best treatment involves a combination of drugs. The research workers in India have shown, and their results are statistically supported, that diodoquin is the most successful single drug, but even it is best used in combination with others.

Emetine has long been regarded as the sheet anchor in the treatment of amœbiasis. In hepatic amœbiasis and granulomata it remains so, given as hydrochloride by injection; in amœbic dysentery we have used the hydrochloride only sparingly and preferred emetine bismuth iodide for such cases.

Chiniofonum, yatren, and quinoxyl were used as 2½ per cent. enemata. Their use has now been largely discontinued because of the parallel preparation, diodoquin, already mentioned. This is diidohydroxy quinoline and is employed in doses of 9 tablets or upwards per day for twenty days.

Arsenical preparations (Carbarsone, Stovarsol, and Amibiarsan) were employed in the combined course of treatment, but their value appeared to be less than that of the other drugs employed.

The complete scheme of treatment used is given in Table II.

TABLE II

*Alternative Schemes of Treatment for Primary Attack of Amœbic Dysentery*

- |   |   |
|---|---|
| 1. Days 1 and 2 . . . . .                                 | Emetine hydrochloride grain 1 by injection.   |
| Days 1 to 20 (inclusive) . . . . .                        | Diodoquin, 5 tablets morning and afternoon, <i>i.e.</i> 10 tablets daily.   |
| Days 3 to 14 (inclusive) . . . . .                        | Emetine bismuth iodide, nightly grains 2 for Indian troops, grains 3 for British troops.  |
| Days 15 to 20 (inclusive) . . . . .                       | Amibiarsan (carbarsone, stovarsol) 1 tablet thrice daily.   |
| Days 24 to 26 . . . . .                                   | Sigmoidoscopy and examination of stools.  |
| Days 41 to 48 . . . . .                                   | Repeat stool clearance tests. If the bowel mucosa at the first examination appeared unhealthy sigmoidoscopy should be repeated at this stage. |
| 2. Days 1 and 2 . . . . .                                 | Emetine hydrochloride grain 1 by injection.   |
| Days 3 to 14 (inclusive) . . . . .                        | Emetine bismuth iodide nightly grains 2 or 3.   |
| Days 5 to 14 . . . . .                                    | Chiniofonum (quinoxyl, yatren) retention enemata 1-2½ per cent. 200 to 250 c.c. each morning.   |
| Days 15 to 20 (inclusive) . . . . .                       | Amibiarsan (carbarsone, stovarsol) 1 tablet thrice daily.   |
| Days 24 to 26 . . . . .<br>and<br>Days 41 to 48 . . . . . | } As for treatment 1.   |

*Treatment of Chronic (Relapsing) Amœbic Dysentery*

- |                            |  |
|----------------------------|--|
| 3. Days 1 to 5 . . . . .   | Sulphasuccidine or sulphaguanidine 5 grams ( <i>i.e.</i> 10 tablets) 6-hourly. |
| Days 1 to 7 . . . . .      | Penicillin 35,000 units 3-hourly.  |
| Days 8 to 27 and follow up | Antiamœbic course 1 or 2 as above.   |

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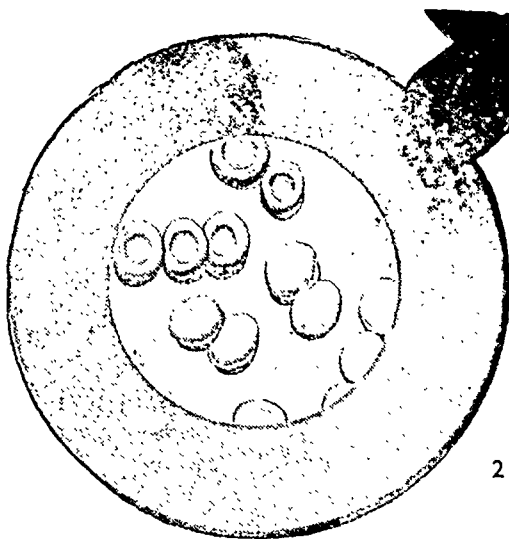
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For the chronic cases the prior inhibition of penicillin and sulphonamide or succinyl sulphonamide proved of great value. This combined therapy acted against the other organisms in the intestine and appeared to facilitate the action of the subsequent course of antiamoebic treatment (Hargreaves, 1946). The scheme of treatment for these chronic cases is also given in Table II.

In the treatment of hepatic amoebiasis with no evidence of intestinal infection, emetine alone was employed, a course of twelve 1 gr. injections being given. After an interval this course, or a shorter one totalling 6 gr., was again given. In a large number of cases this sufficed and aspiration was not called for: in many, however, aspiration was necessary (Cameron and Lawler, 1945). Let me again emphasise that this should be regarded as a medical procedure.

### SPRUE

Sprue was an equally important invaliding disease in the Far East. During 1944, 386 cases returned to Britain with this disability. It is interesting to know that a follow-up of these men indicated that a large proportion were able to return to full duty in this country after treatment. An equally large number recovered following treatment in India and did not require repatriation. I mention this to support a belief that if the case is treated sufficiently early a full recovery can be expected. Papers based on our experience with, and research on, sprue in India have been published by Leishman (1945) and Keele and Bound (1946). They give excellent accounts of the disease and its aetiology. The cases seen in India fell into two groups, those with all the features of the syndrome, and those with steatorrhœa only. In both groups the biochemical findings were identical.

Chronic diarrhœa, cheilosis, glossitis and fissured tongue with loss of weight and energy and flatulent dyspepsia will probably be the picture presented by the returned sufferer. Enquire into the nature of the diarrhœa, and you will find it is of early morning type, and that a pale, bulky and sometimes frothy stool is passed. An increased fat content will most probably be present but we found in India that this was not invariably so in all specimens. We therefore adopted the technique of collecting three successive stools and having them analysed as a single specimen.

Examination of the patient reveals wasting, and in contrast to this a big abdomen, big due to intestinal distension. The mouth region shows angular stomatitis, ulcers inside the mouth, and the characteristic fissured tongue. Anæmia is not a striking feature of many cases; it is present but not to an advanced degree, and it is not invariably hyperchromic and macrocytic. X-ray examination shows "segmentation" and loss of mucosal pattern in the small intestine and marked duodenal delay. With recovery all of these disappear.

A low-fat high-protein diet is necessary in the treatment of these cases. The best additional treatment we found to be liver given as the extract orally, and by injection of the crude liver preparations, not the refined preparations like anahæmin. Equally useful was the daily use of liver soup. Such liver therapy was more successful than the administrations of the pure vitamins, nicotinic acid, riboflavine, and pantothenic acid. Marmite or Vegemite was useful in some cases. Further reports on the value of folic acid in sprue will be awaited with interest. Carruthers (1946) has found it useful in the nutritional diarrhœas in Indian patients—a condition akin to, if not identical with, sprue. In severe cases where wasting was extreme and low plasma protein content and dehydration were features, intravenous administrations of fluids and of plasma were necessary. It was remarkable how little effect infusions of the initial plasma had on the plasma protein concentration. The protein of these appeared to pass to the tissues and only after their needs were met, did plasma administration lead to rise in the plasma protein level. Where achlorhydria or hypochlorhydria was present riboflavine proved useful in restoring acid secretion.

*Giardia (lamblia) intestinalis* may be reported present in stools sent for examination in suspected dysentery or sprue. Most specialists in India will agree that their presence in the intestine can be associated with symptoms, especially in cases where there have been previous intestinal disorders of other causation. Mepacrine is the most effective treatment for giardiasis but it has to be remembered that this condition may be very persistent and account for recurrent bouts of diarrhœa.

I will close with a mere mention of some other conditions you will probably encounter. *Ankylostomiasis* was frequently met and was a common cause of anæmia, which was treated before the parasites were attacked. Ascariasis, and the other bowel infestations also occurred. We found a combined therapy with 3 c.c. of tetrachlor-ethylene and 1 c.c. of oil of chenopodium the most effective against both ankylostomiasis and ascariasis. The use of carbon-tetrachloride was unfortunately attended by fatalities.

*Schistosomiasis* may be encountered among those returned from W. Africa and Egypt. In India we experienced a fairly heavy infestation rate among British troops attached to the 82nd West African Division. A thorough laboratory examination of all personnel was carried out and effective treatment given where necessary. Where the disease is encountered I would advise the use of tartar emetic as therapy in preference to the proprietary preparations.

When *epilepsy* develops for the first time in an adult who has seen service in India think of cysticercosis as the probable cause. Because of the likely prevalence of this condition all cases of epilepsy were evacuated from India as "Convulsions N.Y.D.," unless a history of epilepsy prior to service in India was obtained, or unless a clear cut cause was determined.

*Dracontiasis* or guinea worm disease may be present in a few men returned from West Africa and India. Cellulitis of the lower limbs, or around the penis, is the most likely presenting symptom, and the worm will probably be seen protruding if the part is douched with cold water. Do not try to pull out the worm. Attachment to a match stick to which a turn is given each day is a better line of treatment, unless the whole worm is surgically removed.

*Kala-azar* may prove the cause of unexplained pyrexia. It should be suspected in those returned from the Sudan and from Eastern India showing such pyrexia in conjunction with increasing hepatomegaly and splenomegaly. The association with leukopenia, high blood sedimentation rate, and low plasma protein values will further suggest this disease, and its presence will be established by positive aldehyde and Chopra tests, and the finding of Leishman-Donovan bodies in sternal, splenic, or hepatic puncture material. I prefer urea stibamine for the treatment of *Kala-azar* starting with first dose of 0.1 g., second dose of 0.2 g., and following with subsequent doses of 0.25 g., to a total dosage of 2.5 g.

An interesting condition encountered in India was the *eosinophilic lung*. Its occurrence was practically confined to residents along the sea coast. A high blood eosinophilia (up to 80 per cent. of the white cells), asthmatic symptoms and signs, and a radiological picture showing a snow-storm effect in the lungs, are the salient features. It is pleasing to close on a cheering note—treatment of this condition is very effective, 6 to 8 injections of any arsenical preparation securing cure of most cases. Oral arsenic given as stovarsol, etc. was also reported to be successful.

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## DISCUSSION

*Dr Douglas Robertson* was particularly interested in the remarks about liver abscess. No major tropical condition was so easily over-looked as that. Once the diagnosis is made (and it is not very difficult if kept in mind) there are few diseases so satisfactory to treat as amœbic liver abscess. Results were little short of miraculous after a few (10-12) injections of emetine (gr. i) and aspiration. It was better to give a few doses of emetine before aspiration and then complete the course afterwards.

Another condition of special interest was *Kala-azar*, some cases of which have been treated recently in Edinburgh. *Dr Cameron* had mentioned the formol-gel test, which was a very simple one. Another very simple test

which Dr Robertson had found useful was the globulin test. These tests are easily applied, and afford presumptive evidence of Kala-azar.

*Dr Lamb* said that in a hospital near Liverpool he had had the opportunity of treating about 100 cases of chronic relapsing amœbic dysentery in men returned from India. He agreed about the importance of the psychological aspect in the treatment of such patients as they were very apt to become "bowel conscious." It was a very distressing and depressing condition for the patient and, at the same time, an equally depressing one for the doctor to treat owing to the high relapse rate. It was found that in a carefully controlled series of cases treated with E.B.I., Carbarsone and Quinoxyl enemata the relapse rate was about 90 per cent.

Dr Lamb stressed the importance of adequate follow-up in every case of amœbic dysentery before it could be said that the patient was cured. It was essential to have repeated stool and sigmoidoscopic examinations, and the patient should be kept under observation for at least a year.

*Colonel Cunningham* was particularly interested in what Dr Cameron had to say on dysentery. For two years he had investigated the dysenteries of the native population in East Bengal, where Dr Cameron had been. He had found that the bacillary form was much more prevalent than the amœbic.

Colonel Cunningham referred to cases of benign tertian malaria which he had seen in hospital here where the patients had not developed an acute attack until they reached this country. This was a possibility which should be borne in mind.

*Lt.-Col. Greig* commented upon the increase in knowledge of tropical diseases as a result of the War.

Referring to Leishmaniasis, he said that a line could be drawn down the middle of India roughly from north to south so that to the west you got the local form and to the east the general.

He paid tribute to the important work done by Dr Hamilton Fairlie and colleagues in Australia on mepacrine suppressive treatment of malaria, which they had put on a scientific basis. None of the present day anti-malarial drugs act as true prophylactics. He referred to a new drug, Paludrine—M488, brought out by the I.C.I., which has been tried and found to be curative and non-toxic. Unlike mepacrine it does not cause dermatitis. It should be a great advance in the treatment and prevention of malaria because there is evidence that it is sporozoitecidal, at least for *plasmodium falciparum*, and is thus a true prophylactic in this infection.

*Dr Wright* referred to some investigations on dysentery where it was found that the use of penicillin and sulphasuxadine gave most encouraging results.

With regard to diagnosis, Dr Wright said that the degree of ulceration of the bowel was usually out of proportion to the symptoms. Stool examination was found to be inadequate and he recommended that sigmoidoscopic examination should be carried out in every suspected case.

*Dr Davidson* asked Dr Cameron's opinion regarding the case of a man home from the Middle East whose wife, while on their honeymoon, had developed malaria. She had never been abroad.

*Mr John Bruce* and *Dr Somerville* also took part in the discussion.

*Dr Cameron*, in replying, said he could give no explanation as to the occurrence of malaria in *Dr Davidson's* case.

He thanked *Dr Hill* for clearing up the point as regards the wider prevalence of bacillary than amœbic dysentery. He himself had perhaps not made it quite clear that the figures he quoted were for incidence of carriers, not actual numbers of cases.

*Dr Cameron* was in complete agreement as regards the importance of the psychological factor in chronic diarrhœa. Many cases were of organismal cause, but when this cleared up, became psychological.

*Dr Peterkin* said he agreed with *Lt.-Col. Greig* that there seemed to be definite areas where cutaneous Leishmaniasis occurred while Kala-azar did not. For example, in North Africa many men of a certain division developed Leishmaniasis cutis, but none, so far as he could ascertain, were affected by visceral Leishmaniasis.

# CHEMICAL FACTORS IN PERNICIOUS ANÆMIA

By H. K. KING, M.A., Ph.D., A.R.I.C.

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## I. PERNICIOUS ANÆMIA : ÆTIOLOGY

MINOT and Strauss<sup>1</sup> have dealt recently and authoritatively with the physiological aspects of pernicious anæmia; the present review aims at discussing those aspects of the problem which lie more in the field of the chemist. Nevertheless, a brief survey of the whole field will be included, as this is essential if the chemical data are to be viewed in their proper perspective.

"Anæmia" is a popular rather than a scientific term. It covers a wide range of conditions which appear to be in many cases pathologically unrelated and united only by the single common symptom of a low blood hæmoglobin content. The hæmatological picture may vary widely; the immediate cause may be hæmorrhage, hæmolysis or inadequate hæmopoiesis, and this, in turn, may be only one aspect of some underlying disorder—chronic infection, dietary deficiency, endocrine dysfunction, or even industrial poisoning. However, the anæmia is often the most manifest feature of the syndrome, the most susceptible to quantitative study, and may also constitute the gravest immediate threat to life. There is therefore classified together as anæmia a group of conditions, unrelated either pathologically or ætiologically.

Pernicious anæmia was one of the first of these to be clearly defined when Addison, nearly a hundred years ago, described the disease which now bears his name. Its ultimate cause is still obscure, beyond the establishment of familial tendencies<sup>2</sup> and, though it proceeds if untreated to a fatal termination through a series of apparently spontaneous remissions and relapses, up to twenty years ago no effective treatment was known. Then Minot and Murphy<sup>3</sup> made the classical observation that the condition could be cured by massive feeding of liver—250-500 g. daily. Later, it was found that suitable extracts of liver were effective parenterally in small amounts.<sup>7,8</sup> These clinical observations provided the first clue to the cause of pernicious anæmia. Three years later, our knowledge was greatly extended by Castle's work.<sup>4,5</sup> It was known that pernicious anæmia was accompanied by failure of the gastric secretions, and Castle demonstrated that simultaneous administration of gastric juice from a normal subject together with certain protein foods (*e.g.* beef muscle), produced beneficial results comparable with those obtained with liver; though neither the protein nor the gastric juice were effective *per se*. He suggested

that in the normal stomach an "intrinsic factor," probably a proteolytic enzyme, reacted with an "extrinsic factor" in the dietary proteins to produce a hæmopoietic principle similar to, if not identical with, that present in liver. This substance was presumably absorbed in the intestine, stored in the liver and released from there for transport to the hæmopoietic bone-marrow tissues. This theory is supported by the fact that gastric failure *precedes* the development of the anæmia itself and gastric achylia is frequent in relatives of pernicious anæmia patients.<sup>2</sup>

The hæmopoietic "hormone" (usually referred to as the "liver factor") is therefore regarded as being essential for normal formation of erythrocytes in the bone marrow. When it is deficient, the normal type of erythrocyte (the "normocyte") is no longer produced, its place being taken by a pathological form, the "megalocyte," larger in size and irregular in shape. As these are produced only in much reduced numbers, the erythrocyte count falls from its normal figure of 5,000,000 per mm.<sup>3</sup> to 1,000,000 or even less. Though the increased hæmoglobin content of the megalocyte provides partial compensation, the colour index does not rise above 1.5, so the drop in hæmoglobin content is hardly less disastrous than the fall in the erythrocyte count. Specific treatment, by administration of liver extracts or stomach preparations, results in immediate release from the bone marrow of large numbers of immature erythrocytes, known on account of their characteristic staining reactions as "reticulocytes." A few days after the commencement of treatment these may account for 30 per cent. or more of the total erythrocytes. As they mature to normocytes, this figure falls again to a normal value of 1 per cent. or less. This reticulocyte crisis is widely used for assessing the success of treatment—or the potency of the extract used. It is discussed in detail later.

Failure of the hæmopoietic hormone may arise from causes other than the idiopathic deficiency of the gastric secretions. In rare cases, it has been observed that surgical removal of the secretory region, or its destruction by cancer, produces the same effect. In severe and prolonged dietary deficiency, the stomach may be producing the intrinsic factor but be unable to form the hæmopoietic hormone owing to lack of the dietary extrinsic factor. This is common in the tropics, where the condition is frequently precipitated by pregnancy. The precise relation of this so-called "tropical macrocytic anæmia" to pernicious anæmia is not yet clarified.<sup>6</sup> In pellagra and some intestinal disorders—*e.g.* sprue—interaction of the intrinsic and extrinsic factors is normal, but absorption in the intestine is impaired; or again, in some liver diseases, *e.g.* cirrhosis, the liver may fail to store the hormone. In these megalocytic anæmias injections of liver extracts is helpful, though treatment should aim primarily at relieving the condition causing the anæmia. In the rare condition of achrestic anæmia, formation and storage of the hormone appear to be normal, but utilisation by the hæmopoietic tissues themselves is deficient; the



condition therefore does not respond to treatment with liver preparations and ends fatally.<sup>7, 8, 9</sup> But this and other "refractory megaloblastic anæmias" are now claimed to respond well to proteolysed liver extracts administered orally. It is suggested that these preparations may contain a further factor which is necessary for hæmopoiesis in these conditions.<sup>10</sup> The ultimate cause of pernicious anæmia has yet to be discovered, and attempts to correlate it with other endocrine disorders have led to no conclusive results. Nor is its connection with the common complication of degeneration of the spinal cord understood. This results in loss of sensation in the extremities and weakness in the limbs; the patient may approach the doctor first complaining of "rheumatism" or "sciatica."

## II. ASSAY OF ANTIANÆMIC SUBSTANCES

Viewed from the chemists' standpoint, the problem of pernicious anæmia is no more formidable than many of the vitamin or hormone isolations and syntheses of the past two decades. The comparative slowness of progress is due entirely to one factor—the absence of a satisfactory assay procedure. The only acceptable test involves clinical trial on human cases of pernicious anæmia, which are forthcoming neither in sufficient number to permit more than occasional tests, nor with the uniformity of age, state of nutrition or genetic constitution necessary for the application of the statistical methods so vital for accurate bio-assay. Pernicious anæmia is also an inherently unsuitable condition for such studies; it does not run a steady course, but proceeds by apparently spontaneous relapses and remissions. This necessitates an observation period in hospital of seven days prior to treatment, to ensure that a spontaneous remission, or one stimulated by the rest and diet of the hospital regimen, does not invalidate results.<sup>18</sup> This drastically reduces the number of cases available for the testing of preparations, since many patients are too critically ill on admission to hospital to allow of this delay in treatment. Usually a "satisfactory response" in three cases is taken as evidence that the preparation used is "clinically active" at the dosage given, and in America an official unit, based on this principle, has been adopted.<sup>19</sup> There are separate units for oral and parenteral preparations, the liver factor being about fifty times more active by the latter route. The stomach factor is, of course, suitable only for oral administration. "Satisfactory response" may be defined either in terms of the maximum percentage of reticulocytes attained following treatment, or from the rate of increase in the erythrocyte count. In both cases the response is a function of the original erythrocyte count, and the "satisfactory" values are tabulated for the two methods by *New and Non-official Remedies*<sup>20</sup> and by Dellavida and Dyke<sup>21</sup> respectively. The two criteria do not always give corresponding results. A good reticulocyte response is not always followed by adequate erythrocyte regeneration,

and in any case weak reticulocyte responses may be elicited by a wide variety of non-specific agents, possibly through some irritant action on the bone-marrow cells.

The most urgent problem and the most formidable is the provision of a satisfactory method for assay of the antianæmic factors. The method must satisfy four criteria: (1) Quantitative response to the antianæmic factor; (2) Specificity; (3) Freedom from interference from accompanying impurities; (4) Simplicity and reliability. None of the many methods proposed in the past satisfies these criteria, but a brief survey of these attempts is instructive. The methods may be classified into five groups: (1) Stimulation of blood formation in normal subjects; (2) Cure of experimental anæmias; (3) Biochemical methods; (4) Chemical methods; (5) Tissue culture methods. Some methods are claimed as applicable to both stomach and liver factors, some to only one factor. In most cases it is the liver factor which has been investigated.

(1) The stimulation of hæmopoiesis in normal subjects has been investigated in both man and laboratory animals.<sup>22-29</sup> The usual criteria of activity has been the elicitation of a reticulocyte response, but as non-specific substances ranging from glucose<sup>23</sup> to congo-red<sup>25</sup> appear to be capable of doing this, and as the reticulocyte count is also subject to spontaneous variations,<sup>23, 25, 26</sup> results obtained by this method must be accepted with the greatest caution. The accurate enumeration of reticulocytes is also a difficult technique and failure to realise this may lead to spurious results.<sup>28</sup> Minot and Strauss<sup>1</sup> and Piney<sup>30</sup> discuss in full the effect of antianæmic factors on the blood picture.

(2) Pernicious anæmia has never been observed in experimental animals and attempts to produce it artificially have failed. The obvious method of gastrectomising the animal, and thus depriving it of its source of "intrinsic factor," has been tried without success in dogs;<sup>31, 32, 33</sup> whilst in pigs, pernicious anæmia is said to develop after this treatment, but only after a lapse of two to three years.<sup>34</sup> Results based on attempts to induce anæmias by other methods must be treated with great caution since the anæmias so produced usually bear no pathological relation to true pernicious anæmia. It is true that Whipple's classical researches on blood-regeneration after hæmorrhage stimulated Minot and Murphy's first experiments with liver;<sup>3</sup> but the relation is probably accidental and Whipple's researches,<sup>35-38</sup> valuable though they are in other fields, contribute little to this problem beyond indicating the conditions for rapid blood regeneration once the primary treatment with liver or stomach preparations has been initiated. The tapeworm, *Bothriocephalus*, produces a gastric failure and hæmatological condition similar to that of pernicious anæmia, but the "intrinsic factor" is still secreted and the parasite does not destroy the liver factor, at least *in vitro*.<sup>39, 40</sup> The use of this condition for assaying the anti-pernicious anæmia factors thus rests on a very

uncertain basis. Various poisons have been used in attempts to produce an anæmia responsive to the anti-pernicious anæmia factors, including phenylhydrazine,<sup>41</sup> hydroxylamine,<sup>42</sup> bile acids,<sup>43</sup> bacterial toxins,<sup>44</sup> saponin,<sup>45, 46, 47</sup> and lead.<sup>48-53</sup> Recently it has been suggested that splenectomy, whilst not rendering the animal anæmic, sensitises it so that injection of the liver factor elicits liberation of reticulocytes, and an assay method based on this claim has been described.<sup>54</sup> But these numerous attempts to employ artificial anæmias for the assay of anti-pernicious anæmia potency cannot be said to suggest anything more than that the liver factor may be capable of acting as a hæmopoietic stimulant under very varied conditions. They do not reveal under what conditions, if any, the response is sufficiently consistent, quantitative, and above all, specific to serve as the basis of an assay method.

(3) and (4) The chemical and biochemical methods have found but little favour. Schales' test—determination of the nitrogen in the material precipitated from liver extracts between 70 and 95 per cent. alcohol concentrations—is crude and unspecific.<sup>55</sup> A biochemical test for the liver factor, based on the reduction of methæmoglobin, has been discredited<sup>56</sup> and a like fate has overtaken Lasch's determination of the stomach (intrinsic) factor, based on the proteolytic activity of stomach preparations at neutral *p*H.<sup>57</sup>

(5) Tissue culture methods have the advantage of dealing directly with the hæmopoietic tissue in the bone marrow, and hence are more likely to be specific; on the other hand, they inevitably involve such formidable technical difficulties that only those with special experience of the technique of *in vitro* tissue culture can hope to apply them with success. Three claims have so far been put forward. One<sup>58, 59</sup> is based on the stimulation of the growth of bone-marrow cells by the liver factor. The method is complicated by the fact that, on increasing the concentration of the liver factor, the stimulation rises to a maximum at a critical value and then falls off. Another bone-marrow stimulation method was employed in working out the assay using splectomised animals (see above<sup>54</sup>), but abandoned when the latter technique was perfected. The third method claims to overcome many of the difficulties involved in orthodox methods of *in vitro* culture by using bone-marrow cells suspended in a liquid culture fluid in special vials. It is claimed that bone marrow obtained by sternal puncture from a pernicious anæmia patient retains its pathological structure under these conditions, but returns to the normal type if liver factor is added to the medium.<sup>60-63</sup> None of these tissue culture methods have been confirmed or found their way into general use.

### III. THE INTRINSIC (STOMACH) FACTOR

The function of the stomach factor—also known as "Castle's Intrinsic Factor" or "Hæmopoietin"—has already been described.

It has attracted much less attention than the liver factor, both from the chemist and the clinician, since its use does not extend to so wide a range of megalocytic anæmias; also, more frequent dosage is necessary. It may be administered only orally, and not by injection. A characteristically thermolabile enzyme, it is much less amenable to chemical investigation than the liver factor, which is probably a polypeptide. It is found in different parts of the stomach—the fundus and cardiac regions in man,<sup>11</sup> but the pylorus in the hog,<sup>11, 12</sup> whilst horse<sup>13</sup> and dog<sup>14</sup> stomachs are reported inactive. The commercial preparations comprise the appropriate part of the stomach dried under conditions which do not destroy the thermolabile enzyme. A more refined product is obtained by expressing the juice from the tissue under high pressures, precipitating the hæmopoietin along with the pepsin by addition of alcohol and removing the pepsin by isoelectric precipitation.<sup>64</sup> The stomach factor prepared thus shows the characteristic properties of a protein. It has been claimed to be a proteolytic enzyme, but the difficulty of completely eliminating pepsin and also trypsin, regurgitated from the intestine, has prevented conclusive demonstration of any specific proteolytic activity of the hæmopoietin itself. An assay method based on this supposed proteolytic action has been discredited.<sup>57</sup> Since this work, newer concepts of proteinase specificity have been developed<sup>71, 72</sup> and a study of the action of hæmopoietin on synthetic peptides suggested that the enzyme is a prolinase or prolidase, hydrolising specifically prolyl peptides, with a pH optimum at 6.0.<sup>70</sup> But another worker, employing hæmopoietin from intestinal mucosa, regards the enzyme as an aminopolypeptidase.<sup>73</sup> Our precise knowledge both of the nature and the mode of action of the intrinsic factor is thus very limited. As in every phase of the pernicious anæmia problem, lack of a satisfactory method of assaying antianæmic potency is the stumbling block to future progress. Nevertheless, the intrinsic factor has attracted less attention than it deserves.

#### IV. THE EXTRINSIC FACTOR

Equally limited is our knowledge of the extrinsic factor<sup>4, 5</sup> with which the intrinsic factor reacts in the normal stomach to produce the hæmopoietic hormone found in the liver. Castle<sup>74</sup> recently reported its presence in a wide range of protein foods—milk, eggs, liver, yeast, rice-polishings and wheat germ, in addition to beef muscle—and he reports that it is extracted by dilute acetic acid and resists autoclaving. Sixty-five per cent. alcohol extracts it from casein. This and similar observations have suggested to some workers that the extrinsic factor may be not a protein as first considered, but a member of the vitamin B complex. None of the known B vitamins, alone or in combination, can replace the extrinsic factor however.<sup>74</sup> Also, if the extrinsic factor is not a protein derivative it is difficult to imagine how it reacts with the intrinsic factor which, as far as the evidence goes, is probably

a proteolytic enzyme, to fabricate the liver factor, which in turn is considered to be a polypeptide. Wills<sup>6</sup> considers that an unidentified factor of the B<sub>2</sub> group is involved in the so-called "tropical anæmia," a megalocytic anæmia due to dietary deficiency. But though it is frequently assumed that this condition is analogous to pernicious anæmia save that the extrinsic and not the intrinsic factor is deficient, Wills herself considers that the two conditions are not identical and makes no claim that her results are applicable to pernicious anæmia.

## V. THE LIVER FACTOR

The attempts to isolate the anti-pernicious anæmia factor of liver account for the bulk of the chemical work, starting right from the time of Minot's discovery of liver treatment for the disease.<sup>76</sup> But even now it is not certain whether the modern highly active extracts are representative of the active principle, or consist mainly of inert material containing only traces of a still more intensely active substance. Much of the recent work has been done in commercial laboratories and methods of preparation and isolation are concealed. Cohn<sup>77</sup> early prepared the product known as "Fraction G" by heating the aqueous extract of minced liver to 80° C. at pH 4-5 to denature and coagulate the proteins, and fractionally precipitating the filtrate with alcohol; the active fraction was collected between 50-95 per cent. alcohol concentrations. This process was used in the manufacture of the well-known Eli Lilly "Liver Extract 343." Much of this classical work is now of only historical interest, since "Fraction G" contained only a small percentage of active material and the properties described are mostly those of the accompanying impurities. He established, however, that the factor was comparatively thermostable, though labile towards alkali, and precipitated by phosphotungstic acid but not by the majority of protein precipitants. He suggested that it might be a nitrogenous base or a polypeptide.

Shortly afterwards Gänsölen introduced a liver extract suitable for injection<sup>78</sup> under the trade name "Campolon." The mode of preparation was exceedingly simple—a press juice of liver was rendered free of proteins (which may cause "allergic" reactions) by heat-coagulation. As the liver factor is some fifty times more potent when administered parenterally than orally, this injectable extract enormously simplified treatment, an occasional injection taking the place of massive feeding with liver. At the same time it greatly stimulated research into the nature of the active factor, since crude extracts of the "Campolon" type sometimes produce severe reactions in the patient, and the preparation of the liver factor in a more purified form would reduce both the frequency of the injections and the risk of reactions. Felix and Frühwein<sup>79</sup> found the factor to be precipitable by heavy metals—Ag, Cu, Pb and Hg, the last proving the most satisfactory. But the most important papers were those of Dakin and his

co-workers.<sup>80, 81</sup> They employed salting-out with ammonium sulphate, sodium chloride and magnesium sulphate, and included a precipitation with Reinecke's salt. Their preparations, representing about 0.1 per cent. of the original liver (wet weight) initiated recovery in doses of the order of 50 mg. parenterally, as compared with the 500 g. of liver taken orally in Minot's original treatment ten years before. They describe their product as "a peptide, possessing some, but by no means all, the properties of an albumose." It was free of carbohydrate, yielded 15 per cent. N, two-thirds of which was liberated as free amino-N on acid hydrolysis. Nevertheless, the material failed to give a biuret reaction. Ultrafiltration methods suggested a molecular weight in the range 2000-5000. This process was the basis of the first "refined" extract, "Anahæmin."

Meanwhile Laland and Klem<sup>82</sup> had introduced a very different method. They observed that the liver factor was soluble in phenol; they adsorbed the material on charcoal and eluted with phenol. This, too, has become the basis of a commercial preparation. The claims that this material initiated recovery in doses of the order of a few milligrams<sup>83</sup> were not confirmed, and, in a comparative trial, it proved to be of the same order of activity as Dakin and West's material.<sup>84, 85</sup> Recently, a modification of this method, no details of which are disclosed, claims satisfactory responses to doses of the order of 5 mg.<sup>86</sup> or even less.<sup>99</sup> The use of phenol for eluting the adsorbed material involves difficulties, especially on a large scale, and some workers have tried dilute alcohol as an alternative.<sup>87, 88, 89</sup> Subbarow's product, representing only 2 mg. per 100 g. liver, initiated recovery on injection of 20 mg. Containing 13 per cent. N, four-fifths of which was liberated as free amino-N on acid hydrolysis, it yet failed to give a biuret reaction. Later, however, Subbarow reverted to phenol as eluent,<sup>90</sup> claiming to reduce his effective dose to 7 mg. But it must be emphasised again that the clinical method of assaying potency is inherently inaccurate, and the utmost caution should be exercised in comparing the active doses claimed by different workers in different laboratories.

Subbarow claimed that the liver factor is multiple in nature, the interaction of four factors being required for antianæmic action, viz. a "primary factor" of unknown nature, and three "secondary factors"—*L*-tyrosine, a peptide, and a complex purine. It is difficult to understand how so common a dietary constituent as *L*-tyrosine could play a specific part in the antianæmic complex, or how injection of minute amounts of this amino-acid should be necessary for anti-anæmic response. Another claim that the antianæmic principle may be separated into two parts, active together but not separately, is based on electrophoretic experiments,<sup>91</sup> but a more recent electrophoretic study indicates that the factor is homogenous under these conditions.<sup>92</sup>

Omission of all details of preparative methods renders Karrer's

papers of relatively little value.<sup>93-96</sup> He mentions absorption on charcoal and elution with phenol, and the removal of unspecified impurities by extraction with pyridine. He admits his material is not homogenous. It contained 14 per cent. N, two-thirds being liberated as amino-N on acid hydrolysis, but only 2 per cent. by tryptic digestion. The biuret reaction is described as "doubtful." The preparation was free of P, S, reducing sugars, flavines and pterines. An incomplete investigation of the amino-acids indicated that tyrosine was present but histidine, glycine, phenylalanine, proline and tryptophane absent. Molecular weight determinations by diffusion methods suggested three components with molecular weights of the order 3000, 6500 and 15,000 respectively, as compared with Dakin's figure of 2000-5000 and Mazza's<sup>97</sup> of 3000-4000. Tschesch and Wolf<sup>98</sup> prepared a product whose general properties followed those already described.

Our knowledge of the chemical factors involved in pernicious anæmia is thus extremely sketchy. Many authors, doubtless for commercial reasons, fail to describe their preparative methods adequately, and the preparations themselves are never homogenous and may indeed contain only a small proportion of the active substance itself. Were it not that the materials prepared by quite different methods share in common the general characteristics of a polypeptide, there would be strong grounds for regarding the properties described as appertaining not to the antianæmic factor but to the inert material masking it. The problem of isolation is probably one of separating a number of polypeptides closely resembling each other in physical and chemical properties. But even this is not certain; and a further complication is introduced by the suggestion that several factors may be jointly required for antianæmic action. In every direction, progress is blocked by the absence of an assay method other than that of human clinical trial—slow, difficult to perform, severely limited by the clinical material available, and giving results of barely more than qualitative significance. The solution of the chemical problem waits on the biological.

Whilst this review was in course of preparation, claims appeared that synthetic crystalline folic acid, administered parenterally in doses of the order of 100-500 mg., initiated hæmatological and clinical remission in both pernicious anæmia<sup>15, 16</sup> and in Sprue.<sup>17</sup> Folic acid, a member of the vitamin B group, is found in liver. The molecule includes xanthopterin<sup>100</sup> and recent work claims to correlate anti-anæmic potency with pterine content in liver extracts.<sup>101</sup> It will be noted that the dosage used is considerably higher than that required to produce remission with the most active liver preparations. If, however, these claims are substantiated, our views on the chemistry of the liver factor may require drastic revision.

## VI. SUMMARY AND CONCLUSIONS

Pernicious anæmia is a megalocytic anæmia. Idiopathic failure of the stomach to produce an "intrinsic factor," which normally interacts with a dietary "intrinsic factor," prevents formation of the "liver factor," a hormone which is stored in the liver and is essential for the production of normal erythrocytes. Similar conditions may result from other causes, preventing normal supply of this hormone to the erythropoietic bone-marrow tissue. The condition may be treated by oral or parenteral administration of concentrates of the hormone prepared from liver, or by oral administration of stomach preparations, which replace the deficient "intrinsic factor."

Progress in isolating and investigating the chemical factors involved has been seriously impeded by the lack of any adequate means of assaying antianæmic potency.

The intrinsic (gastric) factor is a typically thermolabile protein, possibly a proteolytic enzyme. The nature of the intrinsic (dietary) factor is unknown.

Various methods of fractionating the liver factor yield material which exhibits high clinical potency, but is probably grossly impure. The liver factor is relatively thermostable; the available evidence suggests a polypeptide structure.

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## NEW BOOKS

*A Manual of Tomography.* By M. WEINBREN, B.S.C.(S.A.), M.R.C.S.(ENG.), L.R.C.P. (LOND.), F.O.R.(LOND.), D.M.R.E.(CAMB.). Pp. viii+270. 397 illustrations. London: H. K. Lewis & Co. Ltd. 1946. Price 45s. net.

Tomography, the radiographic projection of plane sections of the body, has now been practised for a sufficient period to estimate its sphere of usefulness in radio-diagnosis.

In this volume Dr Weinbren gives an authoritative account of the application of this method in the investigation of disease in various systems of the body: the section dealing with the use of tomography in diseases of the chest is particularly convincing and the reproduction of the tomographs is excellent.

There is no doubt that this specialised examination will be used to an increasing extent in the future and a tomographic equipment should be available in any modern X-ray department. To those who are interested either in the problems of diagnosis where tomography is of value or in the details of the practical application of this method of examination, Dr Weinbren's book will be of exceptional interest and value.

*The Care of the Neurosurgical Patient.* By ERNEST SACHS. Pp. 268, with 177 illustrations. London: Henry Kimpton. 1945. Price 30s. net.

Dr Sachs has recognised the need for a presentation in book form of the many details of pre- and post-operative care which require meticulous attention if the work of the neurological surgeon is to be attended with success. The author has based his book on the experience and practice of his own clinic and we cannot avoid an impression that the work would have benefited by a wider survey.

The author merits praise for his initiative and for his very readable presentation of the subject matter. This is no dull book and bears on nearly every page some evidence of the author's engaging personality.

The numerous illustrations, printing and binding are excellent.

*Introduction to Clinical Neurology.* By GORDON HOLMES, M.D., F.R.S. Pp. vii+183, with 37 figures. Edinburgh: E. & S. Livingstone Ltd. Price 12s. 6d. net.

The aim of this work is "to discuss the nature and the significance of the symptoms and abnormal physical signs which a patient with a nervous disorder may present or which may be revealed by clinical examination." As might be expected in a work by a very eminent authority, a master of the art, who has contributed much, both to the science and clinical aspects of neurology, the theme is admirably dealt with in the light of the most recent knowledge. The title is perhaps rather misleading for, while the book will be read by the would-be neurological specialist with the greatest profit, and with much interest and appreciation by the experienced neurologist, its content is rather beyond the scope of all but the exceptional under-graduate and general practitioner.

*Diagnosis and Management of the Thoracic Patient.* Edited by CHARLES PHILAMORE BAILEY, M.D. Pp. ix+334, illustrated. London: J. B. Lippincott Company. 1945. Price 24s. net.

This volume is one of the American Practitioner Series, and consists of a series of fourteen articles which were published in the February 1945 issue of *Clinics*. The subject matter of the articles indicates the field covered—Pulmonary Resection in Tuberculosis, Closed Intrapleural Pneumonolysis, Phrenicotomy, Thoracoplasty, Cavernostomy in Pulmonary Tuberculosis, Primary Bronchogenic Carcinoma, Thoracic Tumours, Transthoracic Gastrectomy and Œsophagectomy for Carcinoma

of Stomach and Œsophagus, A Clinic on the Anterior Mediastinum, Bronchiectasis, Bronchoscopy, Acute Putrid Lung Abscess, Primary Wound Closure in Operations for Chronic Empyema, and Anaesthesia in Thoracic Surgery. The first nine articles constitute a series of monographs of great value to all who are interested in the treatment of chest diseases, and for them alone the book should find a place in the library of the specialist as well as of the less specialised. The detailed statistical analyses of results alone are valuable. Indications for treatment, preparation of patients for operation, operative technique, and after-care are described in detail, and results are assessed critically. Extensive bibliographies accompany each article. The remaining five articles are less ambitious and of more restricted scope, but they round off an excellent symposium.

*Patients and Appendicitis.* By Sir CRISP ENGLISH, K.C.M.G., F.R.C.S., Pp. vii+155, with 4 illustrations. London: J. & A. Churchill Ltd. 1946. Price 10s. 6d.

The author's expressed purpose in writing this monograph is to present an essentially practical treatise on the subject and to stress the importance of treating the patient as well as his disease. The latter aspect is dealt with in the first chapter, which contains much wise advice from which the student and the young doctor will benefit. The remaining eleven chapters deal with the various aspects of appendicitis, acute, subacute and chronic in a complete, if somewhat discursive manner, except that the pathology of the condition is omitted.

As a record of an experienced surgeon's personal views on an important surgical subject, the book is of value.

There is a long bibliography, marred by a number of incomplete references.

*Researches in Normal and Defective Colour Vision.* By W. D. WRIGHT, D.S.C., with a Foreword by L. C. MARTIN, D.S.C. Pp. xvi+383, with 233 illustrations. London: Henry Kimpton. 1946. Price 36s. net.

In his preface the author points out that the researches on colour vision described in this book must be viewed against a physiological background. The subject matter is divided into eight parts and thirty chapters. The first two chapters deal with the visual organ and visual processes, and visual perception respectively, and in chapters III and IV the author's colorimeter and the method of operating it are described. The remaining six parts deal with the luminosity curve, colour mixture, discrimination, adaptation, defective colour vision, and lastly, the fundamental response curves.

Colour vision is admittedly an abstruse and difficult subject and this book is intended for the specialist. The investigations described, which date from 1926, are those of an expert, and this record will be of great value to all who are interested in the subject and an important work of reference. Numerous graphs and diagrams and an excellent index complete an outstanding contribution to one of the most interesting and difficult problems of vision.

*The Diagnosis and Treatment of Pulmonary Tuberculosis.* By MOSES J. STONE, M.D. and PAUL DUFAULT, M.D., F.A.C.P. Pp. 316, with 93 illustrations. London: Henry Kimpton. 1946. Price 17s. 6d. net.

This book covers in a very efficient way the whole subject of pulmonary tuberculosis, and while it suffers necessarily from the condensation which a small book demands, that is offset to a large extent by complete bibliographies at the end of each chapter. It is obviously the product of the authors' wide experience, and they have succeeded in giving a concise, but comprehensive and well-balanced, account of the pathology, diagnosis, and treatment of the disease. There is an excellent and well-illustrated chapter on differential diagnosis, and the chapter on tracheo-bronchial tuberculosis emphasises the significance of that condition in prognosis and treatment. Chapters on tuberculosis in industry and on the social and mental aspects of the management of the tuberculous round off an excellent book. The illustrations are excellent.

## NEW EDITIONS

*A Review of Nursing.* By HELEN F. HANSEN, R.N., M.A. Fifth Edition, revised. Pp. x+854. London: W. B. Saunders Co. Ltd. Price 15s. net.

This book has been prepared with the object of supplying a systematic review of the training received by the nurse. It deals with all the subjects of the curriculum giving an outline of the most important facts in each. A special feature of the book is the attention given to test questions which are set out in various ways. Many of them are written in a form which includes several alternative statements, only one of which can be true. It is very doubtful whether such methods can be of any real service to the student nurse.

*Medical Emergencies.* By C. NEWMAN, M.D., F.R.C.P. Third Edition. London: J. & A. Churchill Ltd. 1946. Price 10s. 6d.

Considerable advances in treatment have appeared since the second edition was issued in 1937 and this has necessitated a good deal of revision in the text.

The author defines an emergency as a condition in which accurate diagnosis and prompt treatment are necessary in order to save life or prevent great suffering and he points out that medical emergencies are urgent indeed. He has chosen the methods he considers the best and simplest and gives them dogmatically and without alternatives, so as to suggest a definite line of action when help is sought. The text has been kept as short as possible so that the essential facts may be readily found in an emergency.

The book can be thoroughly recommended to all practitioners of medicine.

*Ante-Natal and Post-Natal Care.* By F. J. BROWNE. Sixth Edition. Pp. viii+644. London: J. & A. Churchill Ltd. 1946. Price 25s.

F. J. Browne's *Ante-Natal and Post-Natal Care*, which has almost become a classic, has now reached its sixth edition. It is well known that the book includes much more than the title would suggest and as it is written in a most practical and readable way it has gained its rightful place in obstetrical literature. It is difficult, though not absolutely impossible, to find any ante-natal condition which has been omitted and very full references are given to all statements made. Of especial interest are the references to the author's own work in the section on the late toxæmias of pregnancy which has been thoroughly revised, as have the sections on venereal disease in pregnancy, the Rh factor, placenta previa and erythroblastosis. New small sections have been added on acroparæsthesia, angular pregnancy and rubella.

*Milk: Production and Control.* By WM. CLUNIE HARVEY, M.D., D.P.H., M.R.SAN.I., and HARRY HILL, F.R.SAN.I., A.M.I.S.E., F.S.I.A. Second Edition. Pp. viii+512, with 211 illustrations. London: H. K. Lewis & Co. Ltd. 1946. Price 37s. 6d. net.

It is a pleasure to welcome the second edition of this authoritative treatise which deals so exhaustively with milk, its production and control. The whole question is discussed systematically in twelve chapters, the book being completed by the inclusion of three useful appendices and an excellent index. The illustrations are many and are well reproduced.

The chapter devoted to a consideration of the cow, its breeds, milk production, and the diseases to which it is liable, does not seem to show the same accuracy as the rest of the book. Apart from this criticism, however, the standard achieved by the authors is high and the information conforms to modern practice, and it can safely be said that no medical officer of health can afford to be without this book.

*Aids to Public Health.* By LLYWELYN ROBERTS, M.D., M.R.C.P., D.P.H. Fifth Edition. Pp. viii+259, with 4 figures. London: Baillière, Tindall and Cox. 1946. Price 6s.

An extraordinary amount of useful and accurate information is conveyed in this compact little book. Though the conception of Public Health or Social Medicine alters almost daily, its elements receive adequate mention here. A helpful bibliography and good index complete a handbook which can be recommended to medical students.

*Developmental Anatomy.* A textbook and Laboratory Manual of Embryology. By LESLIE BRAINERD AREY, PH.D., SC.D., LL.D. Fifth Edition. Pp. ix+616, with 590 illustrations. Philadelphia and London: W. B. Saunders Company. 1946. Price 35s.

In the fifth edition of this well-known book, Part I on General Development (Embryogeny, Fœtal Membranes, etc.) has been wholly rewritten to incorporate new material—including some account of the very early stages of human development described by Hertig and Rock—and there are 186 new illustrations. The subject-matter has been rearranged in more convenient form, so that there are now 23 instead of 19 chapters; but in spite of all these changes the book has suffered no increase in size, an achievement on the part of the author that merits approbation.

Part II (Special Development) and Part III (Laboratory study of chick and pig embryos) remain substantially the same, changes being chiefly corrective in relation to new information. The whole book, reset in new type throughout, may be recommended as an up-to-date and attractive exposition of Human Embryology.

## BOOKS RECEIVED

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| BELL, E. T. Renal Diseases. Fifth Edition . . . . . ( <i>Henry Kimpton, London</i> )   | 35s. net.     |
| BROWNE, F. J., M.D., D.S.C., F.R.C.S.E., F.R.C.O.G. Advice to the Expectant Mother on the Care of her Health and that of her Child. Eighth Edition. . . . . ( <i>E. &amp; S. Livingstone Ltd., Edinburgh</i> )   | 9d. net.      |
| DUBOS, RENE J. The Bacterial Cell. Second Edition. . . . . ( <i>Harvard University Press, U.S.A.</i> )   | 28s. net.     |
| FLETCHER, ERNEST. Medical Disorders of the Locomotive System including the Rheumatic Diseases . . . . . ( <i>E. &amp; S. Livingstone Ltd., Edinburgh</i> )   | 45s. net.     |
| HADEN, RUSSELL L. Principles of Hematology. Third Edition. . . . . ( <i>Henry Kimpton, London</i> )  | 25s. net.     |
| HARRIES, E. H. R. and M. MITMAN. Clinical Practice in Infectious Diseases. Third Edition . . . . . ( <i>E. &amp; S. Livingstone Ltd., Edinburgh</i> )  | 22s. 6d. net. |
| KERSHAW, JOHN D. An Approach to Social Medicine. . . . . ( <i>Baillière, Tindall &amp; Cox, London, W.C. 2</i> )   | 15s. net.     |
| KLAPMAN, J. W. Group Psychotherapy . . . . . ( <i>Wm. Heinemann Ltd., London</i> )   | 21s. net.     |
| LEITHAUSER, DANIEL J. Early Ambulation. . . . . ( <i>Charles C. Thomas, U.S.A.</i> )   | \$4.50        |
| PEEL FITZGERALD, ALBERT A. Diseases of the Heart and Circulation. First Edition . . . . . ( <i>Oxford University Press</i> )   | 35s. net.     |
| SPIVACK, JULIUS L. Urgent Surgery . . . . . ( <i>Charles C. Thomas, U.S.A.</i> )   | \$10.00       |
| WALSHE, F. M. R. Diseases of the Nervous System. Fifth Edition. . . . . ( <i>E. &amp; S. Livingstone Ltd., Edinburgh</i> )   | 16s. net.     |
| WALSHE, F. M. R., M.D., D.S.C., F.R.C.P., F.R.S., HON.D.S.C. On the Contribution of Clinical Study to the Physiology of the Cerebral Motor Cortex. The Victor Horsley Memorial Lecture, 1946. . . . . ( <i>E. &amp; S. Livingstone Ltd., Edinburgh</i> ) | 1s. 6d. net.  |
| WINTROBE, MAXWELL M. Clinical Hematology. Second Edition. . . . . ( <i>Henry Kimpton, London</i> )   | 55s. net.     |

# Edinburgh Medical Journal

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## THE ÆTIOLOGY AND DIAGNOSIS OF AMŒBIASIS \*

By R. M. MURRAY-LYON, M.D., F.R.C.P.Ed.

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**ÆTIOLOGY.**—Amœbiasis is primarily an intestinal disease but there may be secondary involvement of the liver and more rarely of the lungs and other organs. It is caused by the tissue parasite *E. histolytica* which gains entrance into the body through the ingestion of contaminated food or water. Although chiefly a disease of the tropics and sub-tropics, where it has proved one of the major problems of the medical services, it is widespread throughout the temperate regions. In fact, individuals infected with *E. histolytica* have been found throughout the world wherever surveys have been made. With the return to this country of many thousands of men from hyperendemic areas the recognition of the condition is of growing importance. The correct diagnosis and treatment of amœbiasis is not only essential for the well-being of those returning with the infection, but is necessary for the prevention of its spread to the general population through the passage of cysts. Cyst-passers may be known to have previously suffered from amœbic dysentery and to have been apparently cured, or they may at no time have shown signs or symptoms of intestinal disease. The term "healthy carrier" is most unfortunate because all available evidence indicates that *E. histolytica* always invades the tissues of its host, although the carrier may be symptom-free at the time the infection is discovered (Bercovitz, 1944). Similarly Adams (1945) considers it advisable to regard every intestinal infection with *E. histolytica* as pathogenic. The disease is spread by the contamination of foodstuffs by the hands and finger-nails of cyst-passers, by means of house flies which can pass cysts unchanged through their intestinal canals, and by the pollution of drinking water supplies. The large Chicago outbreak of 1933 which resulted in 1409 proved cases was caused by the pollution of a drinking-water tank by sewage leakage. The incidence of carriers among the staffs of the two hotels

\* A Honyman Gillespie Lecture given in the Royal Infirmary on 22nd August 1946.

whose sewage polluted the common water supply was as high as 37·8 and 47·4 per cent. In those countries where human excreta are used for manure, infection is commonly acquired through the consumption of uncooked vegetables. In the Far East the spread of the disease is probably mostly by means of flies, and the high standard of sanitation in this country is the chief factor limiting the spread of amœbiasis. *E. histolytica* can exist in three forms—the active trophozoite, a precystic form, and as a fully developed cyst. Only this latter can survive any length of time outside the body of the human host. Cysts, however, can live for as long as three weeks and can resist ordinary disinfectants to a remarkable degree, and are unharmed by the routine chlorination of water (Yorke and Adams, 1926). Boiling drinking water and cooking all food is the only safe procedure in endemic areas in the tropics. A patient with acute amœbic dysentery who is only passing active trophozoites is no danger to the community. True epidemics of amœbic dysentery therefore do not occur.

**PATHOLOGY.**—After their ingestion with contaminated food or drink, cysts of *E. histolytica* pass through the stomach to the small intestine. Trophozoites are then liberated from the cysts and invade the mucosa. The cæcum is the chief site for this invasion, but the lower ileum is said to be attacked also. This invasion is facilitated by the motility of the amœbæ and by the cytotoxin which they excrete. They penetrate down to the submucosa and settle down to live on the surrounding tissues, where they are found in a gelatinous substance composed of debris from broken-down cells and mucus. An early lesion consists of a minute nodule which is shown on section to be flask-shaped with its expanded base in the submucosa and a narrow neck leading up to the surface of the mucosa. The body is capable of compensating for the damage done by the amœbæ and so a state of equilibrium may be established. There may thus be only minimal lesions and the infected individual may be symptom-free. Some trophozoites may, however, pass through the precystic stage, form cyst walls and be passed in the fæces whenever the local conditions are not favourable for the amœbæ. For local or general reasons not understood the destructive process may at any time advance more rapidly than the body can repair, and when this occurs there will be spread of the disease process with the appearance or recrudescence of symptoms. Necrosis of the superficial mucosa gives rise to small ulcers with a surrounding zone of œdema and hyperæmia with lymphocytic infiltration. If the process continues these ulcers extend down to the muscular coat. Amœbic ulcers are characteristically raised from the surface of the mucosa and have thickened edges which are undermined. The floors of recently formed ulcers are covered with shaggy necrotic material whilst older ulcers tend to have smooth bases. At any stage repair may take place by granulation tissue and epithelium grows in from the edges to cover the area. This may leave no sign

or there may be a typical shallow depression with a shiny base or an obvious scar. If the infection spreads, sinuses are formed which connect one ulcer with another underneath apparently healthy mucosa. This disease process may be found in the cæcum, at the flexures of the colon and in the sigmoid and rectum. When the process is of long standing the whole bowel wall becomes thickened and fibrosed. This change may be patchy and limited to the cæcum or the whole length of the colon may be involved. The picture may be altered by the amount of secondary infection also present. Thus localised masses of granulomatous tissue may be formed in the submucosa and may in time involve all the layers of the bowel wall. Such an amœboma with varying proportions of fibrous and necrotic tissue may be found in the rectum or, less commonly, in the cæcum or other point in the colon. It may take the form of a fungating cauliflower mass or simulate an annular carcinoma or tuberculoma. The true diagnosis can only be made by histological examination and the co-existence of carcinoma and amœboma has been reported (Morgan, 1944). Ulceration may occasionally proceed to perforation of the gut with resultant general peritonitis or, more often, the formation of a walled-off peri-colic abscess. Another possibility is the erosion of a blood vessel with gross hæmorrhage. This is, however, not common as there is thrombosis of the vessels in ulcerated areas. Chronic cases of very long standing sometimes develop cicatricial stenosis of the colon particularly in its more distal parts.

Microscopic sections of invaded tissues show that amœbæ frequently penetrate the lumina of small veins. Thus trophozoites can readily be carried to the liver in the portal blood stream. The liver cells offer considerable resistance to the amœbæ or liver involvement would be an even commoner complication than it actually is. When trophozoites do manage to establish themselves in the liver they cause liquefaction necrosis of the liver cells in the area with a surrounding zone of hyperæmia. Scattered areas of this kind give rise to the clinical picture of amœbic hepatitis. When either the resistance of the liver is reduced, or the numbers of amœbæ reaching the liver are very high, such areas may extend and coalesce with the formation of an amœbic abscess. The fibrous framework of the liver resists the cytolysin and fibrous tissue is laid down to wall off the cavity. In an uncomplicated case an amœbic abscess contains no pus but only the typical chocolate material composed of shreds of necrotic liver tissue, blood and cytolysed cells. The active trophozoites are found in the walls of the cavity. If, however, there is a bacterial infection, which may be anaerobic, the abscess will contain pus in addition. Amœbic abscess of the liver is most usually solitary, in about 80 per cent. of any large series, though two or three may be present. In the tropics, however, multiple abscesses are sometimes found at post-mortem in fulminating cases. A typical liver abscess is most frequently situated at the upper pole of the right lobe of the liver. The diaphragm is



frequently involved with subsequent rupture of the abscess into the right lung. Owing to the formation of adhesions the pleural cavity is often sealed off and so not infected when rupture takes place. The lung may also be the seat of an amœbic abscess by direct blood spread without clinical evidence of liver involvement, but this is a much less common occurrence. Such an abscess can be situated at any point in either lung and not necessarily in the right lower lobe. The other sites of secondary amœbic infection are very uncommon and need only be mentioned in passing. A critical review by Watson (1945) has emphasised the rarity of urinary amœbiasis, and the invasion of the skin or gall-bladder, or a brain abscess are also unusual complications. These latter complications, apart from brain abscess, are usually the result of a direct spread of the infection to neighbouring tissues and organs, often following surgical operations.

**SYMPTOMATOLOGY.**—As can be seen from a consideration of the pathological changes a very varied clinical picture can be produced. The infected subject may be indistinguishable from a normal healthy person or he may suffer from a fatal illness, and between these two extreme conditions all intermediate stages may occur (Hargreaves, 1946). It has been pointed out that any diagnosis from simple indigestion to cancer is compatible with the varied symptomatology of intestinal amœbiasis. Chronicity is its most important feature and Manson-Bahr (1944) has reported that the disease can last thirty to forty years. Less than 1 per cent. show fulminating manifestations of dysentery, and in the majority the picture is atypical (Sawitz, 1943). It is unfortunate that the term "amœbic dysentery" has become in the minds of many medical men a synonym for amœbiasis, since the majority of cases do not show dysenteric symptoms and therefore may be mis-diagnosed through lack of proper investigation.

The onset of symptoms may follow the ingestion of cysts within a few days or be postponed for months or years. Acute dysenteric symptoms are unlikely to be met with often in this country, though abscess of the liver may present itself as an acute illness without a history of previous ill-health. In acute amœbic dysentery the patient usually passes in the twenty-four hours ten or more copious dark motions which contain mucus and blood, and have a foul smell. In contradistinction to bacillary infections there is usually an absence of marked fever, toxæmia or tenesmus. Occasionally a case will show these features and only be correctly diagnosed when it fails to respond to sulphonamide therapy. In the tropics a double infection is not uncommon and a bacillary infection may light up a latent amœbiasis. Cramp-like pain may be localised to the cæcum or sigmoid regions or may be generalised over the abdomen. In cases which have had a latent infection palpation may reveal thickening of the cæcum or sigmoid.

In chronic amœbic infection diarrhœa is not a leading symptom and many patients, on the contrary, complain of constipation. A

careful history, however, will often elicit the information that there have been occasional short bouts of diarrhoea at irregular intervals. When diarrhoea occurs it may only amount to one or two profuse watery stools or a little mucus may be noticed. The presence of some obvious blood in the stool may be due to bleeding hæmorrhoids which are a very common accompaniment of this disease. This infrequency of diarrhoea as a principal presenting symptom has been noted recently by Bomford (1944) reporting on service patients with proved amœbic infections returning to this country. On palpation of the abdomen thickening of the colon may be made out particularly in the region of the cæcum and sigmoid. Tenderness on deep pressure over these areas is very typical, and Manson-Bahr considers that tenderness elicited over the centre of the sigmoid flexure opposite the anterior superior spine of the ilium is pathognomic of amœbic infection. The patients may complain of actual pain in the abdomen or, more frequently, of vague discomfort. Pain when present is often referred to the right iliac fossa and appendicitis may be simulated. Zachary Cope (1946) has sounded a warning against operating too hurriedly for pain in the right iliac fossa occurring in the tropics, as this may be due to amœbic infection of the cæcum and not to inflammation of the appendix. In the Chicago outbreak 32 cases were operated upon as appendicitis with 13 deaths—a fatality rate of 41 per cent. (Strong, 1942). In amœbic typhlitis the colicky pain may come on after meals through the action of the gastro-colic reflex. On palpation tenderness and resistance may be made out over McBurney's point, but it is frequently rather higher up, and in addition there is often tenderness at the lower border of the liver. The diagnosis can be very difficult even when the possibility of amœbiasis is fully appreciated and, in my own experience, I have seen unnecessary laparotomies carried out as well as seen confidently diagnosed cases of appendicitis settle completely under specific anti-amœbic treatment. Amœbic infection of the appendix does occur, but how often this happens is a debatable point and, unless perforation or abscess formation call for surgical intervention, it is only of academic interest as it requires no modification of routine anti-amœbic treatment. More common than actual pain is a complaint of heaviness or vague abdominal discomfort. This is frequently associated with flatulence and periodic distension of the abdomen when on palpation gaseous distension of the cæcum may be observed. There is usually some anorexia and slight dyspepsia. Less definite symptoms are loss of weight, lassitude and depression. Mental depression of mild degree is very common, and the association of so-called tropical neurasthenia with chronic amœbic infection is well recognised. The condition has to be differentiated from neurosis with bowel symptoms. The symptoms of patients with the latter usually clear up with reassurance after a very thorough investigation, including sigmoidoscopy, has revealed no evidence of organic disease.

The clinical picture of amœbic hepatitis is not absolutely clear-cut so that there is a very marked variation in its reported incidence. Many observers report an incidence of from 5 to 10 per cent., whilst Payne (1945) diagnosed mild amœbic hepatitis in 50 per cent. of his series of a thousand cases in Eastern India. The usual picture is that of a generally unfit sallow-looking individual with a muddy complexion but without actual anæmia. Such a case complains of anorexia, dyspeptic symptoms and constant heaviness or an ache in the epigastrium and right hypochondrium. There may be actual pain over the liver which is sometimes referred to the right shoulder. Low-grade pyrexia is often present. On examination the lower edge of the liver is usually palpable and tender and pain may be elicited by pressure exerted over the lower ribs on the right side. Manson-Bahr states that the association of amœbic hepatitis and jaundice is rarely found, but I have seen slight icterus quite commonly and once or twice moderately severe jaundice which cleared up rapidly and completely under treatment with emetine. Greene (1944) has also reported jaundice in 10.5 per cent. of cases of amœbic hepatitis.

Such a clinical picture of subacute or chronic hepatitis by gradually increasing severity of symptoms and signs merges in to the picture of acute liver abscess. The development of symptoms referable to an abscess may sometimes be gradual or the patient may suddenly become seriously ill. Amœbic abscess, though commoner in the endemic areas in the East where it occurs in from 2 to 5 per cent. of amœbic infection, may also occur in this country in men without intestinal symptoms. The absence of a definite history of preceding dysentery does not necessarily preclude a diagnosis of amœbic abscess. Ochsner and DeBakey (1939), for example, found in a review of collected cases a history of diarrhœa in two-thirds, and diarrhœa actually present at the time of admission for liver symptoms in only one in five. The symptoms are those already described as being found in amœbic hepatitis but are more severe. The temperature tends to be swinging and there is marked sweating and rapid loss of weight. Pain may be very severe and boring in character and either localised to the liver or referred to the shoulder or through to the back or axilla. Occasionally the first indication may be an acute stabbing pain associated with the rupture of an unsuspected abscess into the lung or peritoneum. There is a leucocytosis of 15,000 to 30,000 with polymorphs only increased up to 70 to 80 per cent. On examination the liver shows more marked enlargement both upwards and downwards and there may be signs at the base of the right lung with unproductive cough suggesting an early pneumonia or pleurisy. Sometimes there is such guarding of the abdominal muscles that the liver cannot be palpated. Abscess ought to be diagnosed before œdema and bulging of the intercostal spaces occur as the abscess "points" to the axilla or elsewhere.

When an amœbic abscess ruptures through the diaphragm into the

lung there is usually acute pain in the affected lung, rigors, cough and the expectoration of the typical chocolate-coloured pus when a bronchus is involved. In the more unusual event of the rupture being into the pleural cavity the signs and symptoms are those of empyæma. In about 15 per cent. of cases of amœbic abscess of the liver the lung or pleura is involved by rupture through the diaphragm.

Primary amœbic abscess of the lung is a much rarer condition, but I have seen two cases in a ward at one time. It accounts for about 14 per cent. of all pleuro-pulmonary amœbic infections (Ochsner and DeBakey, 1939). In these cases the symptoms and signs are atypical and pulmonary tuberculosis or an unresolved pneumonia may be diagnosed. There may be general malaise and deterioration of health with either a low grade or swinging temperature with night sweats. Depending on the site of the abscess there may be pleuritic pain and an accompanying friction rub. Cough and expectoration are constant and hæmoptysis common, but the purulent sputum is not characteristic apart from the possible discovery of trophozoites in it. Dormer and Friedlander (1941) failed to demonstrate amœbæ in their series of cases but found eosinophilia of diagnostic importance.

The symptoms of amœboma will obviously vary according to the situation of the tumour mass. The most common situation for such a growth is in the rectum or sigmoid and the symptoms may be identical with those of carcinoma in this region. The patient usually gives either a history of definite antecedent dysentery or one suggestive of previous amœbic infection. He usually suffers from constipation or alternating constipation and diarrhœa, often with the appearance of streaks of blood and mucus in the stools. He frequently has the feeling of being unable to empty the rectum properly and suffers from tenesmus which is unusual in straightforward amœbic infection. In protracted cases the great loss of weight and strength gives rise to the picture of typical malignant cachexia.

DIAGNOSIS.—The only reliable method of diagnosing amœbic infection is the recovery and identification of the *E. histolytica*. The frequency and rapidity with which a definite diagnosis is made largely depends upon the experience and skill of the microscopist. It is the duty of the clinician, if he does not carry out his own microscopic examinations, to ensure that the most suitable material is sent to the laboratory under the optimum conditions for successful identification. When the search is for trophozoites there is much to be said in favour of bringing the laboratory or at least the microscope to the patient's bedside.

Apart from the actual demonstration of the entamœba in one of its forms, amœbiasis can be diagnosed by a complement fixation test. C. F. Craig (1937), who developed the test, claims that it gives positive results in 90 per cent. of infections, and that it becomes negative when the infection has been successfully eliminated. The test, however, requires to be carried out by an experienced serologist, and other

observers have found it only 70 per cent. reliable (Magath and Meleney, 1940). It cannot therefore be employed at present as a short-cut to diagnosis or replace the painstaking search of repeated specimens for the causative protozoa.

All individuals suffering from any form of amœbic infection harbour active trophozoites in their tissues, but only in a proportion will vegetative forms be recovered and identified. In a large percentage diagnosis will depend upon the discovery of the characteristic cysts. In his Lumleian lectures Manson-Bahr (1941) reviewed 535 cases and showed that diagnosis was made by the discovery of trophozoites in 41·5 per cent., and of cysts in 53·6 per cent., and that in the remaining 4·9 per cent. the entamœbæ were only found on examination of scrapings taken at sigmoidoscopy. When there is diarrhœa and particularly when the more distal portions of the colon are ulcerated active trophozoites ought to be found, whereas a normally passed stool usually only shows cysts. Trophozoites only retain their motility for a very short time after leaving their host so that stools must be examined "hot." Kershaw (1946) goes even further and suggests that the interval between the shedding of the amœba from the ulcer and its discharge per anum is of importance and that the patient should not delay defæcation. Purgation may ensure a rapid passage of the vegetative forms before they have time to degenerate and become less readily recognisable. The specimen must be taken to the laboratory in the actual bed-pan and not transferred to another container. This allows the pathologist to choose the most likely looking part of the specimen, where there may be blood and mucus on the surface, from which to take his sample. The vegetative form of *E. histolytica* is easily identified when fresh specimens are examined on account of its size, the ingested red cells and its characteristic active progressive motility by means of extruding pseudopodia.

In chronic infections when the patient is passing normal stools only cysts will be found. As the cysts may be few in number and scattered in the solid fæces their recognition may be a matter of great difficulty unless a method of concentrating them is employed. Faust *et al.* (1939) by means of the zinc sulphate concentration technique which they introduced found that they doubled the yield of *E. histolytica* cysts discoverable by direct fæcal films. With ordinary iodine stained films of fæces only 40 per cent. results were obtained in infected material. This concentration method of Faust's, or some modification of it, ought always to be employed in the search for cysts, as by this technique the washed cysts can be clearly seen and their detail is not obscured by organisms or other contents of the fæces.

Charcot Leyden crystals are often found in the stools, and though not diagnostic of amœbic infection their presence should encourage further search for amœbæ.

Sigmoidoscopy can be employed as an adjunct to diagnosis or used to assess progress under treatment or in tests for cure. There is a

great divergence of opinion amongst authorities regarding the incidence of lesions visible on sigmoidoscopic examination of individuals with an amœbiasis. On the one hand Craig (1943) says that only in 30 per cent. of infected persons are lesions seen in the rectum and sigmoid as amœbiasis is essentially a disease of the cæcum, whilst on the other hand Manson-Bahr (1943) reports lesions in these areas in 80 per cent. of cases. The majority of observers report visible lesions in from 50 to 70 per cent. of cases. This discrepancy can probably be explained by the varying proportions of more acute cases occurring in different series. During an acute phase of the disease sigmoidoscopic examination is unnecessary for diagnostic purposes as active vegetative forms can readily be found in the stools, and such an examination may cause the patient quite marked discomfort or pain. Perforation may occur when very gross ulceration is present, and such a catastrophe has been reported following sigmoidoscopy. In severe cases the rectum will show typical ulcers which can be readily seen by the simple and safe procedure of proctoscopic examination. The chief diagnostic use of the sigmoidoscope is in the investigation of chronic cases in which the examination of the stools has proved negative or indefinite. In these cases the experience of the investigator is of prime importance because, although occasionally quite characteristic ulcers can be seen, in the majority the lesions may be very small and only appreciated by the trained eye. These less obvious lesions are of various types. There may be scattered discrete petechial hæmorrhages without any ulceration or small patches of œdematous mucosa. These may be scattered over an otherwise healthy looking mucosa or superimposed on a generally reddened and velvety surface. Cropper (1945) describes a pin-point crater situated 3 to 6 inches from the anus as the commonest amœbic lesion. This usually takes the form of a small mound about  $\frac{1}{8}$  inch in diameter projecting from the folds of the mucous membrane and having a minute opening at the apex. The appearance may suggest a little yellow-topped pustule. On scraping these areas with a spoon a little matter may be expressed and on microscopic examination show active trophozoites. In addition to active lesions old ulcer sites may be marked by the presence of small depressed areas. These smaller lesions can often be most satisfactorily seen by smoothing out the surface of the mucosa with the end of the sigmoidoscope when it is being slowly withdrawn.

Another aid to diagnosis which must be mentioned is radiology. This is of particular value in cases of liver abscess where the upward displacement and fixation of the right dome of the diaphragm is often characteristic. X-ray diagnosis in these cases is often the most important and dependable laboratory procedure as preliminary stool examination may be negative, but the need for active treatment be urgent. Yater (1944) believes that thorotrast hepatosplenography is of special value in the diagnosis and accurate localisation of liver abscess, and that it is a safe procedure. Seventy-five c.c. of thorotrast

is injected intravenously and films taken two hours later. The drug is taken up by the reticulo-endothelial cells and the normal liver shows a homogeneous density in which the abscess area shows as less dense.

The most important practical point that must be decided is the number of stool examinations that are necessary to confirm a diagnosis of amœbiasis or exclude its presence. No difficulty arises in the cases with dysenteric symptoms, as under these conditions active trophozoites are readily found and identified if fresh specimens are examined within half-an-hour of their being passed. In such cases the first stool examined is usually positive, and if not, the second or third will be. When, however, chronic cases are being investigated, many more specimens may need to be examined and cysts may only be found after twelve or more have proved negative. Sawitz (1943) claims that 90 per cent. of infections can be diagnosed by the following routine examination: Three normal stools on alternate days examined by the zinc sulphate concentration method; one stool produced by a saline purge; and material obtained by sigmoidoscopic scraping. This should be looked upon as a bare minimum, and when the history and clinical findings are suggestive of amœbiasis, further specimens must be examined both for cysts by the concentration technique and for vegetative forms after salines. In patients in whom a clinical diagnosis of amœbic hepatitis had been made in spite of a few negative stool examinations, I have frequently seen a positive stool obtained after starting emetine treatment, and similarly in pulmonary cases treatment may have to be started before the diagnosis is confirmed by the microscope.

### SUMMARY

As amœbiasis can present such a variable clinical picture, without any constant outstanding diagnostic feature, its recognition is largely dependent upon whether the clinician is sufficiently alert to the possibility of its presence or not. With the return to this country of so many men who may be infected, it is important that amœbiasis should be considered more often in differential diagnosis. The fact that diarrhœa is not an essential feature of the disease is not sufficiently appreciated, and the misconception that amœbic dysentery is a synonym of amœbiasis is too prevalent. Diagnosis demands very close collaboration between the clinician and the laboratory, and success depends upon the careful and repeated examination of the stools or other material under optimum conditions. The type of technique employed must be varied according to the activity of the disease at the time of examination. Sigmoidoscopy is an extremely valuable adjunct to diagnosis, especially in experienced hands, and it is important that the small and less obvious lesions be carefully looked for as well as typical ulcers.

# THE ÆTIOLOGY AND DIAGNOSIS OF AMŒBIASIS

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## AMŒBIASIS \*

By J. D. S. CAMERON, C.B.E., M.D., F.R.C.P.E.

AMŒBIASIS was a major problem of the war in the Far East. Its treatment in the early years was one of our failures for which we, in India, were rightly subjected to criticisms from the United Kingdom. Up to a point this condemnation was deserved—for a time we were complacent—we listened to the “pundits of the past” and were beguiled into adopting the treatment they advocated. For a time we failed to grasp the magnitude of the problem. We saw malaria as our Enemy No. 1, while all the time this equally great foe was before us. All our preventive measures and diagnostic prowess were directed towards malaria, its preventive elimination, and its treatment. Success attended these measures to an outstanding degree. We did not marshal our forces to the same extent against amœbiasis, yet amœbiasis is the more serious disease. Each attack leaves the patient in poorer physical condition, and each attack renders cure less likely. We failed to appreciate the importance of this point; we were not sufficiently amœbic-conscious at the time when the patient first complained of diarrhœa, abdominal pain, or other symptom; we did not put accurate diagnosis in the forefront at the first attack; we were content to accept symptomatic recovery of the first attack as cure of the amœbiasis. We, in India at least, reaped the tares.

It was poor comfort to know that our enemy was having equally discouraging results. From captured documents we ascertained that the disease was widely prevalent among Japanese troops in Burma and that, if possible, it was ignored and left untreated. Like us they were short of essential drugs and so treated only those cases where the need was imperative. Palliative treatment for the diarrhœa was all that was undertaken in the majority. An interesting item of captured intelligence was that the Japanese were using rotunden as their chief treatment, emetine being in very short supply. Rotunden is prepared from the root of *Stephania Rotunda* found in Indo-China. It has a sedative action like phenobarbitone and was also recommended in tuberculosis and asthma. Paradoxically, emetine hydrochloride was the only anti-amœbic drug available to us in India for a long time and to this fact must be attributed a major portion of the responsibility for our failure. Soon we were to realise the truth of Chopra's words (1936): “Emetine is far the most successful immediate line of treatment of an acute attack, but is generally a failure in chronic cases and in carriers.” Our complacent acceptance of emetine as a

\* A Honyman Gillespie lecture given in the Royal Infirmary on 29th August 1946.

specific therapy in amœbiasis led to us forgetting a further fact—amœbiasis is a relapsing disease, and the more often a case relapses the less hopeful is the treatment. This statement is supported by Wright and Coombe's analysis of the cases investigated by them for G.H.Q. India at the Ranchi Research Centre (1946, 1947). These figures were corroborated by Smallwood and his colleagues in the Poona investigation.

Dr Murray-Lyon has already dealt with the diagnosis of amœbiasis in this series. Early diagnosis leading to early initiation of treatment is the *sine qua non* eventuating in cure. At the risk of repeating what is already commonplace to all, let me point to a few necessities.

Diarrhœa was so common in the East that to many a formed stool was a pathological complaint. Colic and associated diarrhœa were passed off lightly and alluded to in a terminology adapted to the area—Gypsy tummy, Delhi belly, and such-like diagnoses, popular with the layman and too frequently accepted by the medical profession, often obscured the onset of insidious amœbiasis. But diarrhœa is not an ever-present symptom in amœbiasis. In many cases constipation is more often present, this being punctuated by short and often mild attacks of looseness of the bowel. We must guard against the tendency to regard amœbiasis as a diarrhœal disease—perhaps an unfortunate development from the terminology of the past, amœbic dysentery.

The presence of a dysenteric bacillary exudate does not exclude amœbiasis. Frequently bacillary dysentery is the spark which lights up amœbiasis, and as frequently it prevents its cure. Is bacillary dysentery, or at least an intestinal infection, a direct factor in the onset of amœbiasis and also in its continuance and resistance to treatment? Carriers of amœbic cysts occur in all climates, yet amœbiasis is predominantly a tropical disease. Does some intestinal infection such as bacillary dysentery permit the entry of the amœbæ into the intestinal wall? Some authorities assert that the entamœba histolytica will not attack an intact intestinal mucosa. Whatever the answer, it must be agreed that the finding of bacillary exudate should not end the bacteriological examination, nor should its absence in a chronic case resisting treatment dictate that a course of sulpha drug is not required. Wright and Coombes found a dysenteric exudate or dysenteric bacilli in 41 per cent. of the 278 cases of amœbiasis they investigated.

Clinical examination plays a large part in the diagnosis of the chronic case. The history is suggestive—often no clearly defined acute attack, frequent bouts of diarrhœa, but “no more than every one gets out here,” pain, either diffuse over the abdomen or localised to definite regions, especially the cæcum, hepatic and splenic flexures and descending colon, and this pain occurring irregularly often with weeks between the attacks. Indeterminate dyspepsia of the flatulent type should always lead to suspicion of chronic amœbiasis. Often the symptomatology and findings are so indefinite that a diagnosis of neurasthenia is the easy way out. A careful examination of the

abdomen will help in the majority of cases, looking for splashing and diffuse tenderness with thickening in the cæcal region, spasticity, thickening and tenderness in the descending colon, granulomatous masses, and slight enlargement and tenderness of the liver. Too often these cases fall into the hands of the psychiatrist or the surgeon without a course of anti-amœbic treatment being given: to the psychiatrist because a diagnosis of neurasthenia is so easily arrived at, and to the surgeon because appendicitis is suggested by the examination of the right iliac fossa. Appendicitis is often a difficulty in the differential diagnosis, but there are two useful aids. The tenderness in appendicitis is much more localised than in amœbiasis where it extends over the cæcum. In a country where the latter is common, diffuse tenderness should negative appendicitis in the majority of cases. A white blood count should always be done. In amœbiasis the count may be

#### AIR REPLACEMENT ASPIRATION OF HEPATIC ABSCESS

FIG. 1.—Lateral view with the patient erect.

FIG. 2.—Lateral view with the patient lying prone.

FIG. 3.—Lateral view with the patient lying supine. Outline of the cavities marked after superimposition of the three plates.

FIG. 4.—A. P. with the patient lying on the right side, air hardly discernible against the vertebral column.

FIG. 5.—A. P. with the patient on the left side.

FIG. 6.—A. P. with the patient upside down. Outline of the cavities marked after superimposition of the plates.

anything up to 12,000, but the rise is not due to neutrophil polymorphs as in appendicitis. A differential white count must always be done in such doubtful cases. Mistaking a granuloma for neoplasm may be another cause of reference to the surgeon. I have seen "malignant disease" of cæcum and rectum yield rapidly to anti-amœbic therapy.

A close liaison between clinician and pathologist is required for successful diagnosis and treatment. All who have Eastern experience are agreed that there should be no delay in the passage of the stool from the patient to the microscope. If the *entamoeba histolytica* is to be identified a "hot stool" must be examined. Even in tropical heat it was early realised that examination more than half-an-hour after the stool was passed was seldom attended by success. Cysts could be found, but not actively motile amœbæ. In the cold climate to which we have returned, and in the doubtful chronic cases we will be handling, the examination of the freshly passed stool assumes even greater importance. All pathologists undertaking this diagnosis should provide facilities for the patient to pass the stool in the laboratory and should be prepared to carry out its immediate examination. Any weak link in this chain of liaison reduces the likelihood of successful treatment. The stools should be examined repeatedly before a negative

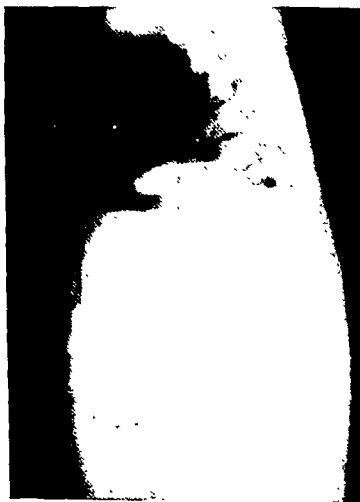


FIG. 1

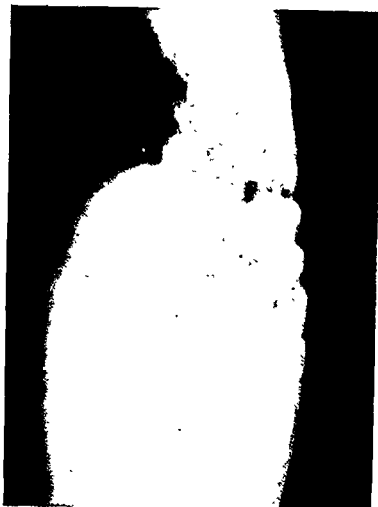


FIG. 2



FIG. 3



FIG. 4



FIG. 5



FIG. 6



diagnosis is accepted. Frequently a stool passed after purgation with, *e.g.* Epsom salts, will yield amœbæ when previous specimens have proved negative. One medical specialist in a West African hospital in India reported that a dose of thymol was often efficacious in this way.

Sigmoidoscopy and proctoscopy are of great importance in diagnosis and treatment. Amœbiasis is in essence a large intestine affection, though Biggam (1930) and others have conclusively demonstrated that the small bowel can also be involved. In most cases the large gut is diffusely attacked, the lower part of the large intestine and the cæcal region being most commonly involved initially. Clark (1925) in an analysis of 186 fatal cases found that 61 per cent. showed ulcers scattered throughout the large intestine, while 34 per cent. showed localised lesions. The localisation of the lesions was in order of frequency (1) cæcum, (2) ascending colon, (3) iliac portion of descending colon, (4) rectum, and (5) hepatic flexure. The appendix was affected in 41 per cent. of the cases. With 61 per cent. of cases showing lesions throughout and the descending colon and rectum high on the list of localised areas, it follows that sigmoidoscopy and proctoscopy must play an important part in diagnosis and in assessment of cure. The sigmoidoscope will for most of you be the instrument of choice, but where it cannot be used I would plead that the proctoscope be not despised. A large number of cases are diagnosable from rectal lesions, and use of the sigmoidoscope will aid misdiagnosis if the rectum is not viewed. The sigmoidoscope must be regarded as a medical instrument and sigmoidoscopy as a medical procedure. In using the sigmoidoscope, just as the pathologist must be careful not to diagnose all amœbæ and cysts as *entamœba histolytica*, so must the clinician beware of diagnosing all abnormal areas as amœbic ulcers and pre-ulcer states. Sigmoidoscopy has a double place in therapy, it frequently provides the early diagnosis, while at the end of treatment it is essential for the assessment of cure and the prevention of relapse.

Amœbiasis is primarily an intestinal infestation, but dissemination may take place to other situations in the body. The liver is the commonest of these; amœbic hepatitis is present in a very large number of cases, in a few abscess formation occurs. The liver lesion follows the passage of the amœbæ into the intestinal blood and so by the portal vein to the liver. Typical necrotic changes occur in the liver substance with formation of an abscess or abscesses of varying size. Some may reach an enormous size and even reduce the liver tissue to a thin shell surrounding the abscess cavity. Similar lesions may develop in the lungs, either primary, or secondary to rupture of a hepatic abscess. The brain is a less common situation. I have also seen cases of amœbiasis affecting the female genital tract and the skin. In all of these situations active *entamœbæ* are present without cystic and precystic forms, a point of importance when their treatment is considered.

Emetine is deservedly the first drug we turn to when we consider the treatment of amœbiasis. "Ipecacuanha is first mentioned in Purchas' *Pilgrimes* in 1625. Introduced to Paris in 1672, it was used as a secret remedy by Helvetius in 1680 and was financially backed by King Louis XIV. The first reference to emetine is by Bardsley in *Hospital Facts and Observations*, London, 1830. . . . Vedder in 1911 demonstrated the amœbicidal properties of Emetine and in the succeeding three years Leonard Rogers standardised its use in amœbic dysentery" (Callender, 1927). At first received enthusiastically, and therefore too much relied on, emetine hydrochloride is now regarded as a valuable agent but not the unfailing remedy originally claimed. Its proper use is in the acute stage where it has a dramatic effect in allaying symptoms. But symptomatic relief is not cure, and so emetine hydrochloride has to be followed by other amœbicides. Chopra summarises the position: "Theoretically, emetine should be an ideal drug against amœbiasis. . . . In actual practice, however, it has not proved uniformly satisfactory and a large number of cases relapse. It is said that emetine cures about one-third of the cases, one-third apparently improve, in the remaining one-third the drug has no effect at all. . . . The reason for this failure in some cases is the fact that, although emetine acts on the amœbæ lodged in the tissues of the intestinal wall, it has no effect on the parasites in the lumen of the gut. . . . The deeply situated organisms are only reached by the emetine through the blood stream. Unfortunately, in long-standing cases fibrosis is set up and the capillaries are cut off, thus preventing access to the parasites by the drug circulating in the blood. Entamœbæ lying in the necrotic or fibrous tissue (which is avascular) are thus able to escape the action of emetine." This was exactly our experience in India. In 1941 and 1942 emetine hydrochloride was virtually the only amœbicide available and we used it in full faith. Relapse after relapse was our reward. Fortunately other amœbicidal drugs then became procurable.

Emetine bismuth iodide (E.B.I.) is an insoluble powder containing 25 to 28 per cent. emetine and 18 per cent. bismuth in the form of the double iodide, which liberates active emetine in the intestine. Care must be taken in the administration of E.B.I. to guard against liberation in the stomach and yet ensure that the active agent is freed in the small intestine. Gelatine capsules were found to be the most suitable vehicle. Hardened and coated pills and tablets frequently passed through the bowel unchanged. It is a mistake to reduce the dose or cease the treatment because E.B.I. is producing nausea or sickness. These symptoms are prerequisites of successful therapy. They indicate, not liberation in the stomach, but action in the intestine, and for this the drug was administered. The absence of these symptoms should cast doubts upon the efficacy of the therapy. To lessen their intensity two procedures are recommended—abstinence from food for at least three hours prior to administration, and a

sedative such as luminal grain 1, or tinct. opii minims x to xv one hour before the E.B.I.

I have no experience of two other emetine compounds—emetine periodide and auremetine. Emetine periodide contains 38·7 per cent. emetine and 61·3 per cent. iodine; auremetine 28 per cent. emetine, 16 per cent. auramine and 56 per cent. iodine. Both are claimed to be less toxic than E.B.I., but general opinion is that they are also less efficacious. Graham Willmore and Martindale (1926) and Adams (1944, 1945) speak of the value of auremetine, but a critical trial carried out by Lindsay Lamb and Royston (1945) did not support these views.

It has to be recalled that emetine is toxic to the host as well as to the parasites. Two systems are especially susceptible, the cardiovascular and the nervous systems. A lowering of the blood pressure is the commonest initial sign of affection of the former and myocardial affection and irregularities may follow. Neuritis with pain, weakness, and paralysis is the chief nervous manifestation. The cumulative effect of emetine has to be remembered when second and subsequent courses are planned. The toxic action of emetine is doubted by some; it is not by those of us who have had to deal with a large number of cases, especially among small-built, ill-nourished, and anæmic Indian troops.

Kurchi bismuth iodide and other preparations from kurchi bark enjoyed a local reputation as amœbicides in India. We did not find them of high value.

Quinoline preparations are the common associates of emetine in treatment. As solitary therapeutic agents they have proved no more successful than emetine, but have shown great value in combined therapy. Their amœbicidal action appears to be attributable to the iodine content.

The iodine-oxyquinoline-sulphonic acid preparations (yatren, chiniofonum, and quinoxyl) contain 26 to 28 per cent. of iodine and may be administered either orally or rectally. Orally they are given as 4-gr. pills, while rectally 8 ozs. of 1 to 2½ per cent. solution are given as a retention enema following preliminary bowel lavage with a pint of 2 per cent. sodium bicarbonate solution. Stronger solutions than 2½ per cent. may be employed, but they are irritant to many patients and so cannot be retained for the desired six to eight hours. As Manson-Bahr (1944) has pointed out, careful administration and positioning of the patient are necessary to secure good results.

Entero-vioform (iodochlorhydroxyquinoline) contains about 40 per cent. iodine and 12 per cent. chlorine. Given as 4-gr. capsules it is claimed, especially by continental physicians, to be more effective than the above preparations. Its irritant action renders it unsuitable for rectal administration.

The latest addition to this group is undoubtedly the most active. Diodoquin (diiodohydroxyquinoline) was highly recommended by



American workers and was employed by Wright and Coombes at Ranchi and by Smallwood and his colleagues at Poona. Both teams of workers were enthusiastic in their reports on its value, their results corroborating those obtained by the American workers when used in conjunction with other amœbicides. They did not obtain as successful results when diodoquin was used alone. Diodoquin is issued in 3·2-gr. tablets and in the Indian investigation 9 to 12 tablets were given daily. Smallwood (1945) summarised his opinion: "There seems evidence that diodoquin is the best iodine compound and that it ranks high, possibly as high as E.B.I., in therapeutic value. It has the added virtues of being easy to administer, pleasant to take with, practically no toxic effects, and of giving symptomatic relief even to those who are not cured by it." It is a double iodine compound with quinoline, the iodine content of which is 63·9 per cent. as compared with the 26 to 28 per cent. content of the yatren group and 40 per cent. iodine content of entero-vioform. It is the least soluble and least absorbed of the quinoline iodine preparations. Diodoquin is an American preparation but, in this country, diiodohydroxyquinoline is issued by Messrs Thomas Kerfoot. Initial reports indicated that diodoquin was non-toxic even in large doses. Later reports, however, do not confirm this. Silverman and Leslie (1945) quoted three cases of toxicity where twelve tablets were given daily in conjunction with emetine. It is interesting that all three cases were cleared of amœbæ. In India no toxic results were reported. The related chemical composition of these preparations is shown in Fig. 1.

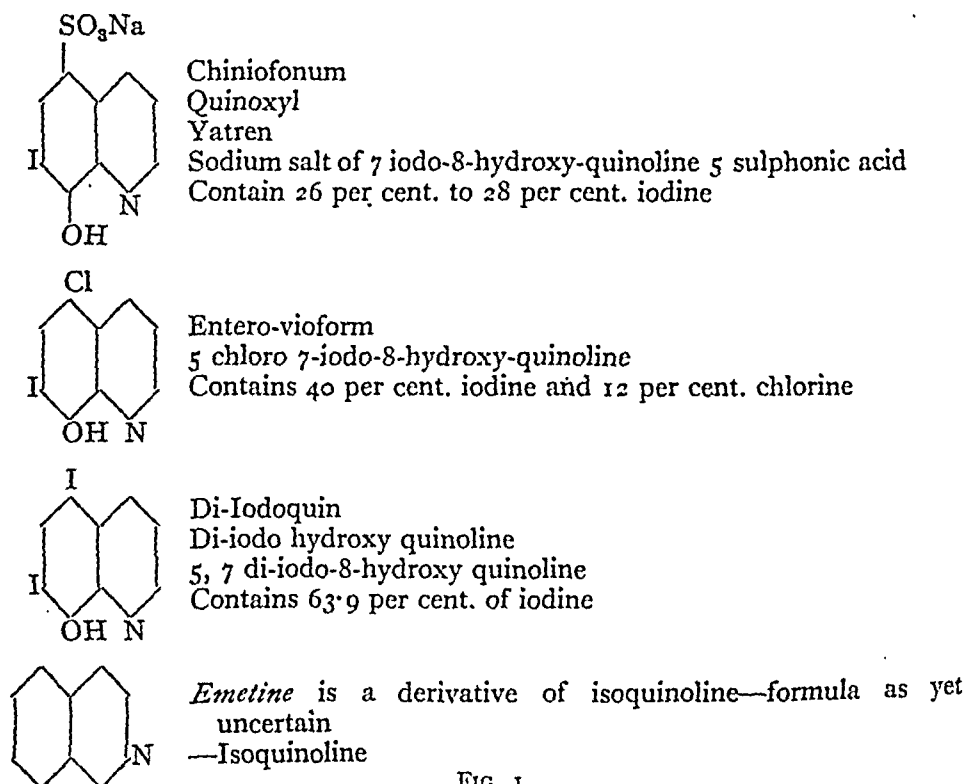


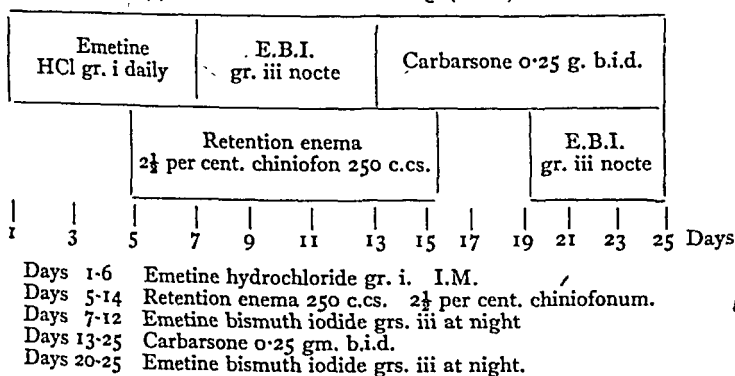
FIG. 1.

Arsenical compounds have been employed as anti-amœbic agents ; stovarsol, carbarsone, and amibiarsone were the three such preparations used in India. Carbarsone was the most universally popular and had a high reputation among the pre-war European population. It could be administered orally in 3-gr. doses twice or thrice daily, or as retention enemata in 2 per cent. solution. We employed it only as an adjuvant to other lines of treatment. As a terminal therapeutic agent it was probably of value for its "tonic effect" more than as an amœbicide.

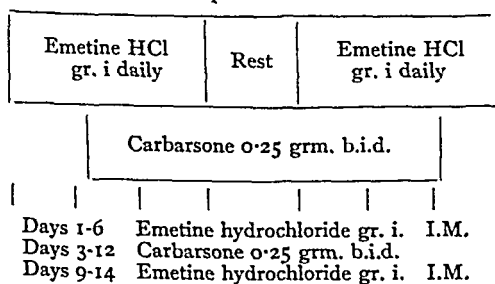
From my remarks on the individual drugs employed it will be obvious that we found no single amœbicide completely effective. Emetine was of extreme value in the control of the acute symptoms

FIG. 2.

## (a) Standard treatment G.H.Q. (India).



## (b) Treatment in use prior to introduction of above.



and in the treatment of the non-intestinal varieties of amœbiasis, but its "cure value" was not high. In one series of cases reported from India, Payne (1945) assessed clinical cure at 33 per cent., improved with occasional relapse 33 per cent., frequent relapses 28.2 per cent., resistant cases 5 per cent., and death 0.8 per cent. This was typical of the experiences in all parts of India in the early stages of the Japanese war. Similarly the iodine quinoline compounds and the arsenical preparations proved equally ineffective. In combination, however, the amœbicides proved much more valuable, and most of

the research undertaken in India was directed towards determining the most successful combinations of these drugs. Based on the early Indian experience and on the reports of other workers, an initial standard treatment was issued in 1944 and this formed the basis both of our subsequent treatment and of our research. In all therapeutic researches this treatment was used as control and all fresh remedies were measured against this yard-stick.

With this treatment improved results were early apparent. The improvement was only partially due to the combination of drugs employed, for a large part of the success was attributable to the discipline it introduced and the thoroughness of attack which developed therefrom. It focussed attention on the need for energetic therapy at the earliest possible moment, but it was open to criticism. Six emetine injections were regarded by some as more than necessary for the control of the acute symptoms; others, including Dobell (1945), considered that its weakness lay in the division of the E.B.I. course into two parts, his opinion being that the minimum unbroken course of E.B.I. should be of 10 days duration. The possibility of toxicity if twelve days of E.B.I. followed on 6 grs. of emetine hydrochloride by injection was the reason that dictated the broken course. The introduction of retention enemata was highly unpopular in some quarters at first, but even this met with fairly general approval eventually. The introduction of enemata more than any other step impressed the importance of the condition and the need for thorough and exhaustive treatment. Perhaps the most vital part of the scheme was the follow-up. After treatment was concluded, it was insisted that each patient should have at least three negative stools and a clear sigmoidoscopy before transfer to convalescent depôt or return to duty. By this means it was ensured that no patient was discharged with an obviously active lesion. Immediately after treatment most cases are free from positive evidence in the stools, three weeks later amœbæ or cysts may be present. Further examinations of stool and, if need be, sigmoidoscopy were therefore ordered at this time. If positive evidence was obtained the patient was then returned for a further treatment course. This follow-up of treatment proved of great value in the prevention of frequent relapses.

Modification of the standard treatment was recommended as the result of the research work at our two centres. Wright and Coombes tested seven groups of treatment. After submitting their results to statistical analysis they concluded that three groups were equally effective (Fig. 3), but recommended that retention enemata of chiniofonum be replaced by oral diodoquin (Fig. 3*b*) to ease the work of an already overburdened nursing staff. They further considered that as their shortened course (Fig. 3*c*) was as effective as the others, and as it took less time, it should be the treatment of choice in acute cases. Smallwood's results were similar but were more emphatically favourable to diodoquin.

Treatment of the chronic case proved the hardest of our tasks. At both centres combination of the acute anti-amœbic course with preliminary sulphaguanidine, or sulphasuccidine, or sulphathiazole, gave only imperfect results. It was at this time that Hargreaves

FIG. 3.

Courses recommended by Wright and Coombes.

Emetine HCl gr. i daily		E.B.I. grs. iii nocte		Carbarsone 0.25 g. b.i.d.																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																					
S'suxidine 65 grms.		Retention enema 2½ per cent. chiniofon 250 c.cs.		E.B.I. grs. iii nocte.																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																					

(a) G.H.Q. (India) standard treatment plus 65 grms. sulphasuxidine.

Emetine HCl gr. i daily	E.B.I. grs. iii nocte	Carbarsone 0.25 g. b.i.d.
Diodoquin tabs. 3 t.i.d.		
S'suxidine 65 grms.		E.B.I. grs. iii nocte

(b) Replacing retention enemata in above with diodoquin.  
3 tabs. (each 3.2 grs.) t.i.d. for 20 days.

Emetine HCl gr. i daily	E.B.I. grs. iii nocte								
Diodoquin tabs. 3 t.i.d.									
S'suxidine 65 grms.									
2	4	6	8	10	12	14	16	18	20 Days

- (c) Days 1-3 Emetine hydrochloride gr. i. I.M. daily. Sulphasuxidine 65 grms.  
 Days 1-20 Diodoquin 3 tabs. (each 3.2 grs.) thrice daily.  
 Days 4-15 Emetine bismuth iodide grs. iii nightly.

(1944) suggested that the need in relapse cases was to rid the gut of secondarily infecting organisms prior to exhibiting amœbicidal drugs. Our attempts to carry this out with sulpha drugs alone had been unsuccessful, but he, acting on the suggestion of General Biggam, combined sulphasuccidine and penicillin with a remarkable degree of success. Both of our Indian research teams immediately adapted this

treatment to our own anti-amœbic course and soon confirmed the value of Hargreaves' work. Sulphasuccidine or sulphaguanidine was given in doses of 20 grms. daily for five days concurrently with penicillin in doses of 35,000 units 3-hourly for seven days to an approximate dosage of 2-mega units.

FIG. 4.

## Recommended treatment for intestinal amœbiasis

## A. Acute cases

Emetine HCl gr. i daily	E.B.I. grs. iii nocte	Carbarsone g. 0.25 b.i.d.
Diodoquin 5 tabs. b.i.d.		
Sulphasuxidine or Sulphaguanidine 100 grms.		
2	4	6
8	10	12
14	16	18
20	22	24
26	Days	

Emetine HCl gr. i. daily	E.B.I. grs. iii nocte	Carbarsone g. 0.25 b.i.d.
Sulphasuxidine or Sulphaguanidine 100 grms.	Retention enema 2½ per cent. chiniofon, 250 c.cs.	

## B. Relapse cases

Penicillin 35,000 units 3-hourly	Emetine HCl gr. i daily	E.B.I. grs. iii nocte	Carbarsone g. 0.25 t.i.d.
Sulphasuxidine 100 grms.	Diodoquin 5 tabs. b.i.d.		
2	4	6	8
10	12	14	16
18	20	22	24
26	28	30	32 Days

Penicillin 35,000 units 3-hourly	Emetine gr. i daily	E.B.I. grs. iii nocte	Carbarsone g. 0.25 t.i.d.
Sulphasuxidine 100 grms.	Retention enema 2½ per cent. chiniofon 250 c.cs.		

Follow up for all cases :—During first week after treatment—3 stools and sigmoidoscopy ;  
third or fourth week after treatment—3 stools and sigmoidoscopy.

Summarising these results, what do I recommend for treatment of cases of amœbic dysentery occurring in this country? Few, if any, will be primary, but for these cases Wright and Coombe's shortened

course is suitable, and if desired could be supplemented with ten days of an arsenical preparation. The follow-up examinations of stool and by sigmoidoscope must be observed as of equal importance with the actual treatment. The vast majority of cases encountered will, however, be relapse cases, and combined penicillin and sulpha therapy must precede the anti-amœbic course. Further, proctitis is a common feature of these cases, and where this is seen at the initial sigmoidoscopic or proctoscopic examination chiniofonum retention enemata may prove valuable. Accordingly, I suggest two alternative courses. In these relapse cases the follow-up observations are particularly necessary, especially three weeks after cessation of therapy. Fig. 4 illustrates the courses of treatment recommended.

The non-intestinal varieties of amœbiasis, hepatic, pulmonary, cerebral, and cutaneous, call for treatment with emetine hydrochloride, for it is in these that emetine achieves its more spectacular successes. A course of 12 grs. should be given, and this should be followed, after a minimum interval of two weeks, by a further 6 grs. if this appears desirable. No other drug is necessary unless there is evidence of an associated intestinal infection when the combined treatment already discussed should be given. On theoretical grounds arsenical preparations are inadvisable if hepatitis is present.

If a sufficiently large amœbic abscess develops, it may be necessary to deal with it by medical aspiration, but this should always be delayed until emetine has been given for at least four days, unless the abscess is on the point of rupture. Even advanced abscesses may subside without aspiration. Open surgical drainage is now discountenanced. "Medical" aspiration should be persisted with unless it is obvious that the abscess is too large to be dealt with in this way, or is increasing in size despite repeated aspiration, or has become secondarily infected. In this last instance, however, it is probable that the use of penicillin has retained infected hepatic abscess as a condition to be treated medically. I was very interested in the case reported by Hunt (1945) which was treated in this way.

The introduction of emetine and other agents into the abscess cavity has been recommended by some physicians. I have not found this of advantage nor necessary in the majority of cases. Emetine hydrochloride by intramuscular injection has sufficed as anti-amœbic agent in most cases.

In conjunction with Lawler (1943) a method of aspiration combined with air replacement was recommended for dealing with hepatic abscesses. This method was widely employed in India. The illustrations I use to demonstrate the method were provided by Davidson and Lawler whose cases have not yet been published.

Amœbiasis is a disease of carriers. "All cases come from cysts, only man passes cysts, all infections come from man" (Napier, 1943)—a statement not entirely accurate but sufficiently so to indicate that the carrier problem is of primary importance. Passage of the amœbæ

themselves plays no part in the spread of the disease and so the acute phase is, for preventive medicine, unimportant. With improvement in the patient's condition the amœbæ are forced to the precystic and cystic forms and so the convalescent becomes the danger. Opinion differs as to the lesion in the asymptomatic carrier—a minimal lesion of the bowel extruding cysts is the view of some, Chopra and others are of opinion that in latent carriers the "*Entamœbæ histolytica* live in the lumen of the gut and feed upon the bacteria there. They never invade the tissues and produce very mild symptoms."

The carrier state calls for treatment in this country. In India carriers were so numerous and drugs so scarce that the policy adopted had to be to ignore carriers unless showing symptoms. In this country no such policy is necessary—all who show cysts in the stool must receive a course of treatment. The two drugs which have been shown to be most effective against cysts are E.B.I. and diodoquin, and full courses of these, either alone or in conjunction, should be given to all carriers. If any dysenteric symptoms are associated with the presence of cysts in the stool the patient must receive the full course of treatment for intestinal amœbiasis.

Diet is a subject of great importance in the treatment of amœbiasis. For too long a regime of semi-starvation was inflicted on patients suffering from any form of dysentery. Such starvation merely tended to continue the dysenteric state. At the acute stage food-intake must be restricted, but as soon as possible a diet of full caloric and vitamin content should be given. Apart from roughage there is no call for restriction of any article of hospital dietary.

Complete bed rest is essential until treatment with all forms of emetine and retention enemata has ceased. This is necessary both for the patient and for his intestine. Rest for the intestine must further be ensured by withholding all laxatives and cathartics. Fortunately, the continuous administration of the salines, magnesium and sodium sulphate, and of castor oil, is no longer fashionable in the treatment of either form of dysentery. Rather is sedative therapy with bismuth, opium, and belladonna to be preferred.

The importance of an optimistic outlook by doctor and nurses in attendance is obvious; patients with chronic dysentery are notoriously of low morale and benefit from even the lightest of psychological uplifts. Show faith in the treatment you are recommending and don't discuss your failures.

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# OUTLET CONTRACTION OF THE PELVIS \*

By W. I. C. MORRIS, M.B., F.R.C.S.E., M.R.C.O.G.

THERE is no great unanimity in regard to the incidence or even the existence of outlet contraction. Stander (1946) states that contractions of the pelvic outlet occur in about 6 per cent. of all women. De Lee (1938) quoted figures as high as 26 per cent. (Stocker), but others, including Bourne and Williams (1939), are sceptical of the importance of outlet contraction, and emphasise that the head which passes the pelvic brim is unlikely to meet grave difficulty at the outlet.

All of us, however, are familiar with the occasional unexpectedly stiff forceps operation, as a result of which we deliver with much soft tissue damage a still-born baby, or, perhaps worse, one which survives to develop signs of grave intra-cranial damage. A tentative diagnosis of outlet contraction in such a case may enable us to lay a flattering unction to our souls, but outlet contraction is a subtle condition which may result from a variety of deformities and abnormalities, and its detection before the occurrence of a disaster is often difficult. I propose to devote the major portion of this lecture to an examination of various diagnostic criteria which may give such forewarning, and to deal but briefly with other aspects of outlet contraction.

## THE SHAPE AND DIMENSIONS OF THE FŒTAL HEAD IN LABOUR

The first approach to this problem should be to obtain an accurate picture of the foetal head in that stage of labour when it first meets the outlet resistance. As clearly demonstrated by Moir (1929, 1932), the head, moulded in the attitude of full flexion, approximates very closely to a cylinder, with bi-parietal, sub-occipito-bregmatic, and occipito-frontal diameters all more or less equal. As a reasonable average the diameter of this cylinder in the full-term head may be taken as 9.3 centimetres ( $3\frac{3}{4}$  inches), and so long as the head remains flexed, this is the largest diameter. During the normal mechanism of extension of the head an oblique measurement (not a true diameter of the cylinder) which we may accept as roughly 10 centimetres (4 inches) has to pass the outlet.

## THE PELVIC OUTLET IN RELATION TO THE FŒTAL HEAD

The foetal head enters the outlet at the inferior pelvic strait or plane of least pelvic dimensions, *i.e.* the plane which cuts the ischial spines, the lower border of the symphysis pubis, and (not infrequently)

\* A Honyman Gillespie Lecture delivered in the Royal Infirmary on 27th June 1946.

the sacro-coccygeal joint. The axis of advance of the foetal head makes a bend almost equal to a right angle at this plane, changing from a downwards and backwards path to one which is downwards and forwards. This change of direction carries the advance into the canal of the outlet proper, bounded at the sides by the medial surfaces of the bodies of the ischia; bounded posteriorly by the soft tissues of the pelvic floor and by the coccyx (a structure which is of negligible importance if normally mobile); and opening anteriorly through the gap between the conjoint rami of ischium and pubis, referred to as the pubic arch. The apex of the pubic arch is closed by the structures of the vestibule.

### TYPES OF OUTLET CONTRACTION

*Bony contraction of the outlet* may result from :—

- (a) Absolute narrowing at the plane of least pelvic dimensions.
- (b) Narrowing below the level of this plane, *i.e.* narrowing of the pubic arch.
- (c) Combinations of the above.

#### *Narrowing of the Plane of Least Pelvic Dimensions*

The first of these contractions may involve either the coronal or the sagittal measurements of the outlet. Williams (quoted Stander, 1946) was more impressed by the frequency of coronal contractions, but Moir (1941) considers narrowing in the sagittal plane to be at least as important. In either case, the narrowing may result from a general funnel tendency reducing the pelvic cavity more or less uniformly from brim to outlet, or on the other hand, the contraction may be an isolated incident. Certain conditions are notoriously associated with general funnelling of the pelvis, *e.g.* the android pelvis (Caldwell, Moloy and D'Esopo, 1933, 1934, 1935), high assimilation pelvis, and spinal deformities such as dorso-lumbar kyphosis and occasionally spondylolisthesis. It is also recognised that the so-called justo-minor contraction of the pelvis is often associated with funnel deformity, which reduces the outlet even more than the brim (Stander, 1946). As an isolated incident, the coronal measurements of the plane may be reduced by prominent ischial spines, inverted into the pelvic cavity, while the antero-posterior diameter may be reduced by unusual convergence of the lower sacrum towards the symphysis pubis, especially in that extremely common abnormality where the sacrum consists of six fused vertebrae.

*Narrowing of the pubic arch* is usually independent of any general alteration of the pelvic shape. The effect of narrowing of the pubic arch is to deny the anterior portion of the bony hiatus to the head. It is as though the symphysis pubis were prolonged downwards and backwards to an extent depending on the degree of narrowing. The

influence of this intangible barrier (Fig. 1) produces a reduction in the available antero-posterior diameter of the outlet canal dependent upon two factors :—

- (a) The extent of the pubic arch denied to the head.
- (b) The angulation between the plane of the pubic arch and the axis of the symphysis pubis. The more nearly this approaches  $180^\circ$ , the less the influence of pubic arch narrowing, and vice versa.

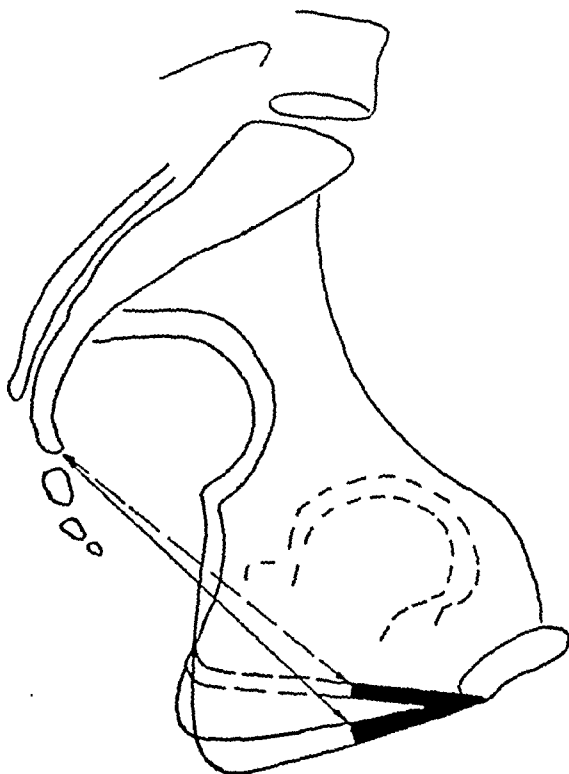


FIG. 1.—Showing effect of varying angle between axis of symphysis and plane of arch.  
Shaded area = portion of arch denied to head.

Besides reducing the available antero-posterior diameter of the outlet, the closure of the anterior portion of the arch alters the general axis of the advance of the head, partially undoing the curve of the birth canal, and compelling the head to emerge more posteriorly than usual. This has two important effects to be referred to later, viz. :—

- (a) The stimulus to internal rotation of the head is diminished (Moir, 1929, 1932).
- (b) Perineal trauma is more common and more severe.

#### MEASUREMENTS OF PELVIC OUTLET IN THE DRIED PELVIS

(a) *Measurements of Least Pelvic Plane.*—Exact definition of the measurements is simple. The antero-posterior diameter is measured between the lower border of the symphysis pubis and the tip of the

sacrum. When one or more pieces of the coccyx are fused with the sacrum, the diameter requires to be measured to the lowest fixed point. The transverse diameter is measured between the tips of the ischial spines. Stander (1946) defines these as :—

Antero-posterior	. . . . .	11·5 centimetres
Transverse	. . . . .	10·5 centimetres

but wide variations occur. It is suggested by Nicholson (1938, 1943) that it is more profitable to calculate the area of this plane as a geometrical ellipse of which the foregoing measurements are the axes, rather than to rely on the linear measurements alone. Radiological studies by Ince and Young (1940) in 500 consecutive women yielded an average figure of 93·7 sq. cm. This can be compared with the area of a cross-section of a 9·3 cm. cylinder, which is approximately 68 sq. cm.

(b) *Measurement of Pubic Arch.*—It is difficult to obtain a satisfactory method of stating the measurement of the arch. The most usual technique is to measure the base of the arch, that is the distance between the ischial tuberosities, and to correlate this with the distance between the mid-point of this diameter and the sacral tip. This is referred to as the posterior sagittal measurement of the outlet. The distance between the inter-tuber-ischial diameter and the symphysis can also be measured and is referred to as the anterior sagittal diameter of the outlet. By applied trigonometry, the quotient of the anterior sagittal diameter by the inter-tuber-ischial diameter can be used to determine the angle subtended at the symphysis pubis by the inter-tuber-ischial diameter (Ince and Young, 1940; Nicholson and Tauber, 1946), and this is sometimes referred to as the sub-pubic angle. It can be measured by more direct means of course. Figures quoted are :—

Inter-tuber-ischial	. . . . .	11 cm.	}(Stander, 1946)
Posterior sagittal	. . . . .	7 cm.-10 cm.	
Sub-pubic angle	. . . . .	80°	
			(Smout, 1943)

These measurements do not provide a very satisfactory index of the capacity of the pubic arch. For example :—

(a) The inter-tuber-ischial diameter is to be measured between quadrilateral bony masses, not between easily defined points, and, even in skeletal material, wide errors are possible (Heyns, 1945). Moreover, if we consider the cylindrical body of the foetal head passing through the pubic arch it will be apparent that any major obstruction will occur where the converging rami become tangential to the cylinder, generally some distance from the tuberosities. If the pubic arch were a strict triangle, a knowledge of the inter-tuber-ischial diameter and the sub-pubic angle would enable us to predict these points with accuracy. However, the conjoint rami of the ischia and pubis are

seldom straight, but show a slight concavity directed medially near the symphysis, and in some cases a convexity towards the middle line in their ischial portions so that each conjoint ramus comes to have a sigmoid curve. The inter-tuber-ischial diameter gives no information as to the possible existence or location of such a convexity.

(b) The sub-pubic angle, however estimated, is of limited value. A narrow angle may be an indication of a narrow base to the pubic arch, but it is quite erroneous to assume that, for any given measurement of the base of the arch, the capacity of the arch is influenced adversely by a narrow angle (Nicholson and Tauber, 1946). The reverse is actually the case, for, if the inter-tuber-ischial diameter remain constant, the area enclosed by the rami is greater with the smaller angle. This appears a paradox, but a moment's reflection reveals its geometrical accuracy (Fig. 2).

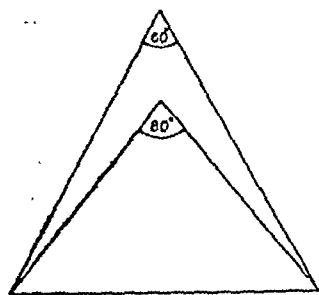


FIG. 2.—Sub-pubic angle.

It is therefore justifiable to fall back on a measuring expedient which is not scorned in engineering, namely, to use a gauge in assessing the calibre of an irregular aperture. Such a gauge would be a cylinder measuring 9.3 centimetres in diameter. In fitting it into the dried pubic arch, note could be taken of two points, namely:—

- (a) The distance between the lower border of the symphysis pubis and the circumference of the cylinder, *i.e.* waste space at apex of pubic arch.
- (b) The distance separating the base of the pubic arch from the parallel diameter of the cylinder.

The former measurement should not exceed 1 centimetre, and in a roomy arch the coronal diameter of the cylinder should be at least 1 centimetre in front of the ischial tuberosities (Figs. 3 and 4).

## MEASUREMENT OF THE PELVIC OUTLET IN THE LIVING SUBJECT

It is now expedient to discuss the measurement of the outlet in the living subject. Two methods are available, clinical and radiological. Since the radiological method bares the bones as it were, it will be profitable to dispose of it first, but not at length, since the subject has been covered so fully in the British literature by Moir (1941), Nicholson (1936, 1938, 1943), Ince and Young (1940), Heyns (1945), Williams and Phillips (1946), Kenny (1944) and Dewar (1946), while the classical American work by Thoms, Caldwell and Moloy is too well known to require comment.

*Radiological Measurement of Pelvic Outlet*

It is desirable to have three views of the pelvis. First-class technique is necessary. For ease of calculation, the metric system offers enormous advantages.

(a) Postero-anterior view of pubic arch taken with the patient sitting well forward with the symphysis pubis in contact with the

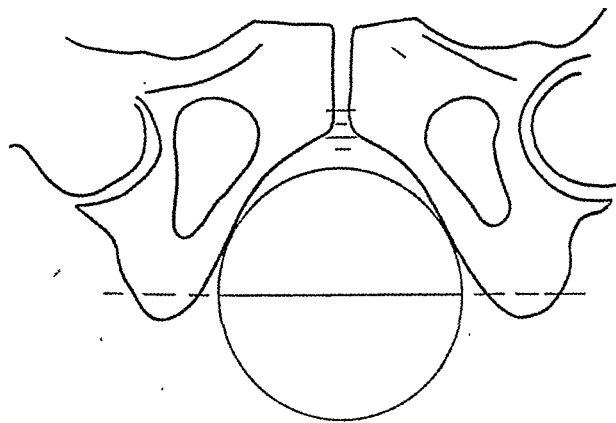


FIG. 3.—Wide arch.

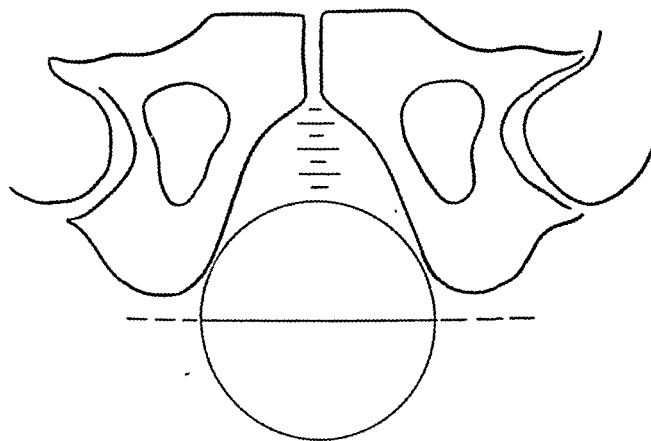


FIG. 4.—Narrow Arch.

cassette, a Lysholm grid intervening. A very accurate projection with minimum distortion can be attained and the inter-tuber-ischial diameter may be read, although the examiner is often in doubt as to which end points to select in making this measurement. More important, however, the shape of the arch is accurately shown, and, by superimposing on the film a transparency on which is outlined a circle of 9.3 centimetre diameter, it is possible to assess the capacity of the arch. The interval in centimetres between the apex of the pubic arch and the circumference of the circle, and the relationship of the coronal diameter of the circle to the ischial tuberosities are noted. The former measurement will be used in assessing the effect of pubic

arch narrowing in relation to the other bony boundaries of the outlet, the latter in assessing the effect of such narrowing upon the soft tissues.

(b) *Lateral*.—The lateral film permits the measurement of the anterior and posterior sagittal measurements of the outlet, and of the antero-posterior diameter of the least pelvic plane; and gives an opportunity for calculating a *corrected antero-posterior outlet diameter* allowing for any narrowing of the pubic arch as follows:—

A point is taken in the general line of the conjoint rami seen in profile, at a distance from the lower border of the symphysis equivalent to that of the waste space recognised in the pubic arch view, and the distance between this point and the tip of the sacrum is taken as the "*Corrected antero-posterior diameter of the outlet*." (See Figs. 5-15.)

(c) Antero-posterior, either in a sitting posture or recumbent with the lumbar spine in lordosis. The diameter between the ischial spines and, in some cases between the medial surfaces of the ischial tuberosities may be measured. This film should be taken before the foetus is sufficiently large to obstruct the X-rays.

#### ILLUSTRATIVE CASES

CASE 1.—Mrs H. Para o. Age 28. (Figs. 5 and 6.)

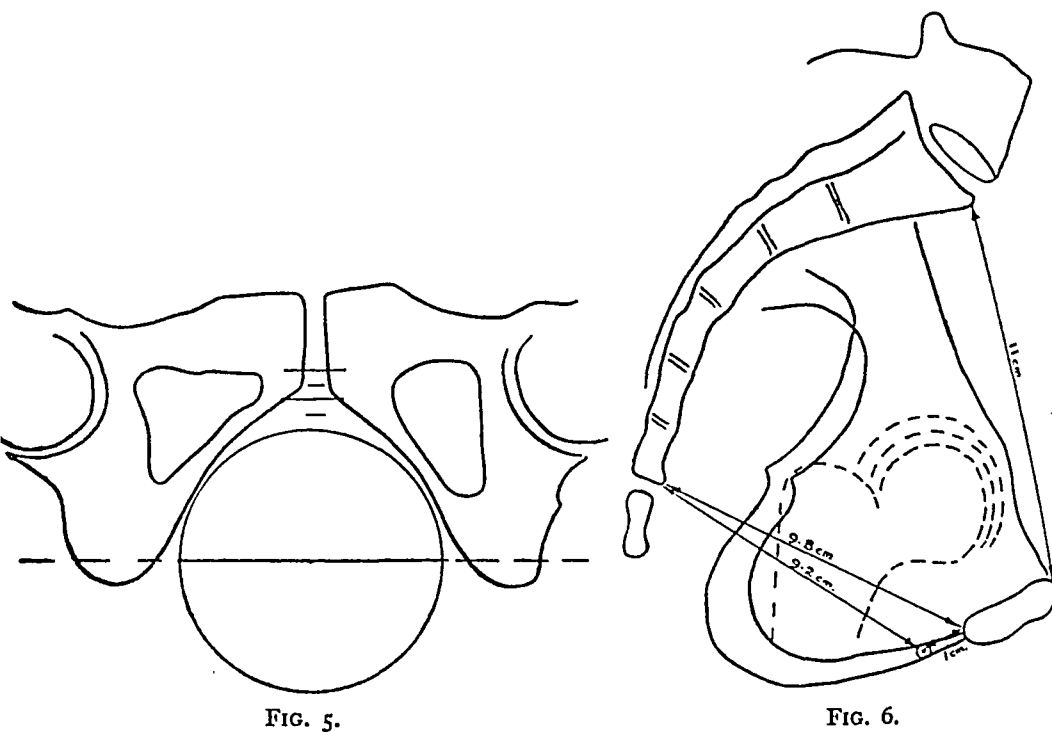


FIG. 5.

FIG. 6.

Outlet contraction due solely to antero-posterior shortening associated with six-segment sacrum. Pubic arch fairly roomy.

Obstetrical conjugate	.	.	.	.	11.0 cm.
Antero-posterior of outlet	.	.	.	.	9.8 cm.
Corrected antero-posterior of outlet	.	.	.	.	9.2 cm.

Low forceps delivery after deep impaction of head in transverse diameter, following twenty-seven hours' labour. Living 6 lb.  $5\frac{1}{2}$  oz. baby. Both survived.

CASE 2.—Mrs McS. Para o. Age 24. (Figs. 7 and 8.)

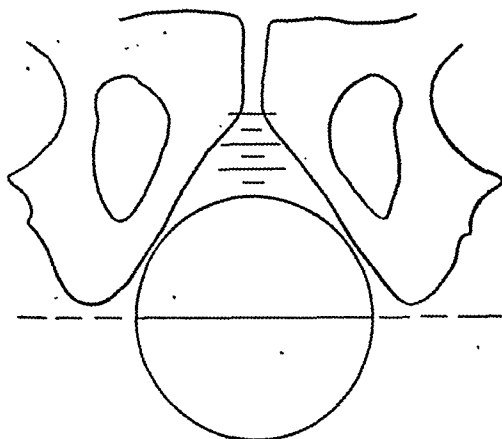


FIG. 7.

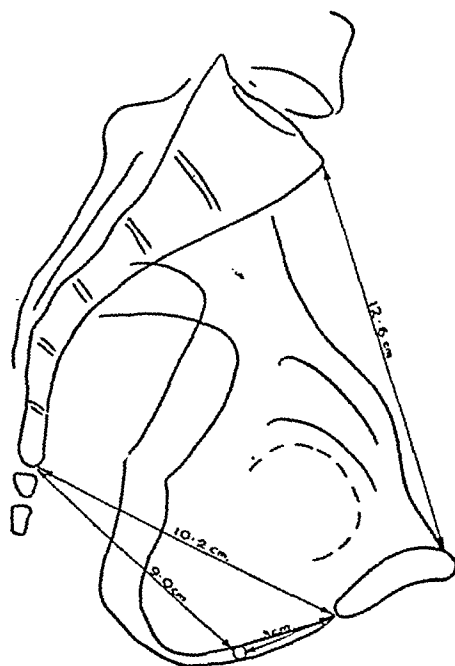


FIG. 8.

Outlet contraction due partially to six-segment sacrum, but principally to narrow arch which shows 3 cm. waste space.

Obstetrical conjugate	.	.	.	12.6 cm.
A.P. of outlet	.	.	.	10.2 cm.
Corrected A.P. outlet	.	.	.	9.0 cm.



Mid forceps delivery after forty-eight hours' labour with head obliquely L.O.A. Living 8 lb. 8 oz. baby. Both survived, but mother suffered severe perineal trauma and was unable to urinate for three weeks after delivery.

CASE 3.—Mrs C. Para 0. Age 29. (Figs. 9, 10 and 11.)

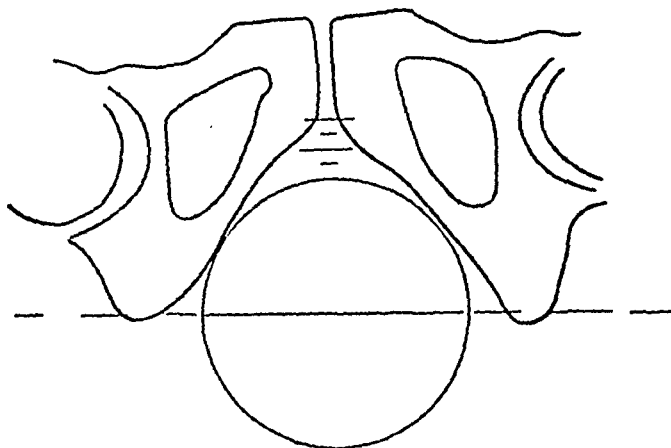


FIG. 9.

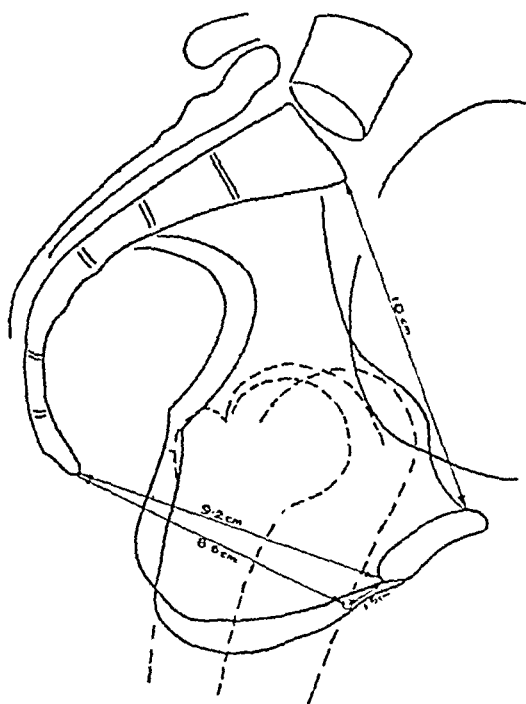


FIG. 10.

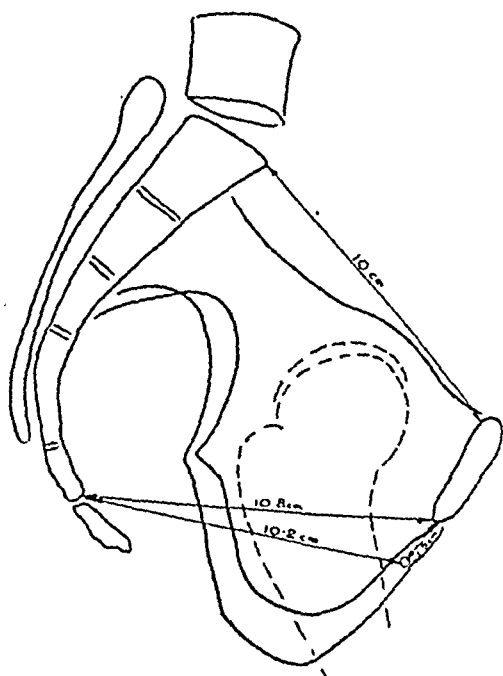


FIG. 11.

Outlet contraction associated (a) with narrow arch due chiefly to convexity of conjoint rami despite wide inter-tuber-ischial diameter, and (b) with complete bony fusion of sacrum and coccyx. Conjugate of brim also small.

Obstetrical conjugate	.	.	.	.	10.0 cm.
A.P. outlet	.	.	.	.	9.2 cm.
Corrected A.P. outlet	.	.	.	.	8.6 cm.

Spontaneous vertex delivery after six and a half hours' labour of 6 lb. 12 $\frac{3}{4}$  oz. baby, in lithotomy position and following deep episiotomy. Both survived. Morbid puerperium. Post-natal pelvic X-ray shows fracture of the sacrococcyx with enlargement of diameters to :—

A.P. outlet	. . . . .	10.8 cm.
Corrected A.P. outlet	. . . . .	10.2 cm.

CASE 4.—Mrs McC. Para 0. Age 40. (Figs. 12 and 13.)

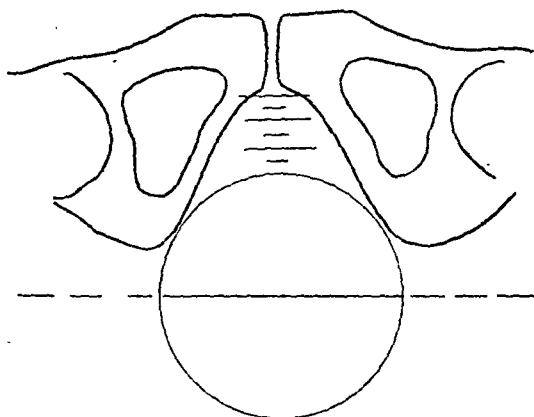


FIG. 12.

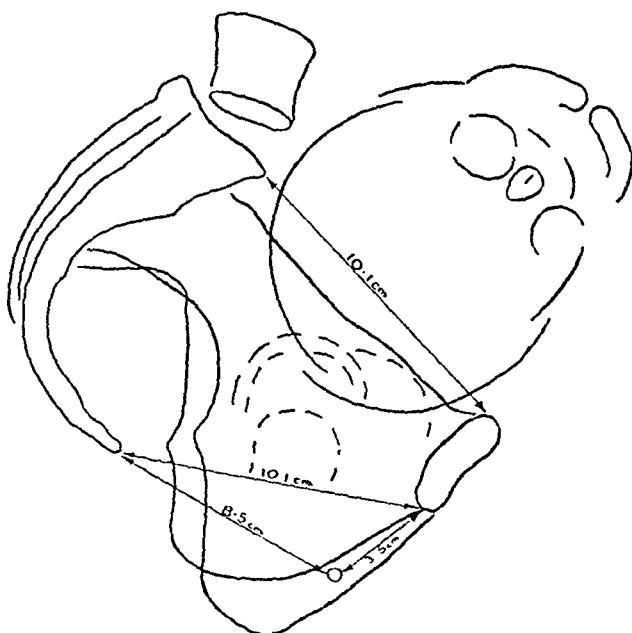


FIG. 13.

Outlet contraction dependent on (a) very gross narrowing of arch,

(b) complete fusion of sacrum and coccyx. Obstetrical conjugate also small.

Obstetrical conjugate	10.1 cm.
A.P. outlet	10.1 cm.
Corrected A.P. outlet	8.5 cm.

After twenty-four hours' labour, head had not passed the brim, despite considerable moulding. Lower segment Cæsarean section. 6 lb. 10 $\frac{3}{4}$  oz. baby. Both survived.

CASE 5.—Mrs McI. Para o. Age 28. (Figs. 14 and 15.)

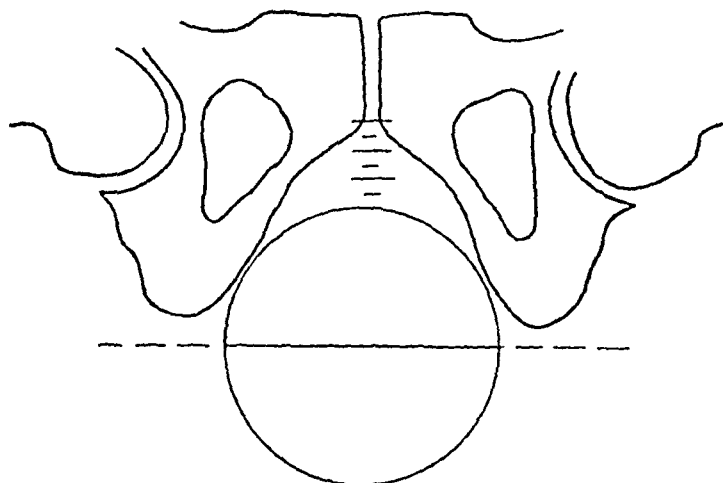


FIG. 14.

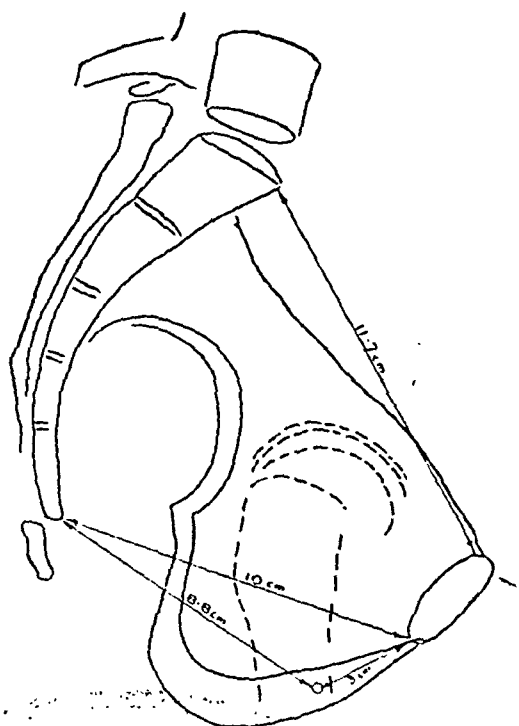


FIG. 15.

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Twins. Outlet contraction dependent upon :—

(a) Narrow arch due to convexity of rami.

(b) Unusual convergence of lower sacrum.

X-rays taken post-natally show dislocation of coccyx.

Obstetrical conjugate	. . . . .	11·7 cm.
A.P. outlet	. . . . .	10·0 cm.
Corrected A.P. outlet	. . . . .	8·8 cm.

Outlet contraction was recognised first in second stage of labour with frank breech impacted after thirty hours on sacral tip—no mobile coccyx present at that time—antero-posterior diameter of least pelvic plane equalled 8 centimetres.

After legs brought down, natural forces delivered trunk of child, but head became completely impacted with long axis in antero-posterior diameter. *Forceps failed to deliver head and slipped off.* After manual rotation to bring sub-occipito-frontal diameter of head into transverse of outlet, head delivered with strong jaw and shoulder traction following bi-lateral episiotomy. 6 lb. 2½ oz. baby still-born. Autopsy showed intra-cranial hæmorrhage and fractured vault of skull. 4 lb. 7½ oz. sister (also breech) delivered alive with head in transverse diameter of outlet. Second twin and mother survived. Puerperium not morbid.

### *Clinical Measurement of the Outlet*

The *routine clinical measurements* of the outlet are :—

(a) The antero-posterior of the least pelvic plane.

(b) The inter-tuber-ischial.

(c) The posterior sagittal.

(d) The anterior sagittal.

In addition attempts are made to form *subjective impressions* of :—

(a) The amplitude of the pubic arch.

(b) The distance between the ischial spines.

(a) *Measurements.*—Of the actual measurements (as distinct from subjective impressions), I believe that the only one which can be taken with any approach to accuracy is the antero-posterior diameter of the least pelvic plane. Two techniques exist. Either the measurement may be made during vaginal examination with the tip of the middle finger in contact with the sacral tip and the knuckle of the index finger opposed to the symphysis pubis, the location of which is marked as in measuring the diagonal conjugate; or alternatively an external measurement may be made with callipers from the lower margin of the symphysis to the lower end of the posterior surface of the sacrum. Whichever technique is adopted, the sacral tip must be identified by moving the coccyx bimanually between vaginal (or rectal) fingers, and the fingers of the examiner's disengaged hand applied

externally in the natal cleft. As pointed out by Moir (1941), the left lateral position is particularly suited to taking these measurements, and the rectum must be empty. With practice one can make the internal measurement very accurately. It is usually very close to the radiological measurement. Any error arising is on the safe side, the measurement being under-estimated by a few millimetres. Heyns (1945) claims that the external is at least as accurate as the X-ray measurement if a deduction of one centimetre be made to allow for the thickness of the sacrum and soft tissues.

I find the inter-tuber-ischial diameter very difficult to measure. Thick skin, firm fat, and a bursa which allows the integument to move most freely over each large quadrilateral mass of bone, make it almost impossible to fix any definite points between which to take the measurement. To find myself differing in successive examinations of the same patient by two centimetres in either direction is no rarity, and a conviction of my fallibility in this respect has led me to abandon all attempts at making this measurement.

The anterior sagittal and posterior sagittal diameters can be estimated only if it is possible to define the point where the inter-tuber-ischial diameter crosses the perineum. I am seldom able to satisfy myself of this and accordingly I do not attempt measurement of these diameters.

(b) *Subjective Impressions*.—So far as subjective impressions are concerned, it is of course undesirable to rely on these, but probably less so than to take fallacious measurements.

(i) *The Pubic Arch*. (a) *External Palpation*.—In a thin patient, palpation of the pubic hiatus with the whole of the volar surfaces of the fingers may enable one to assess the arch as wide or doubtful, but if the patient be at all plump, the difficulties are such as to render this a most fallible observation. A subjective impression of the width of the inter-tuber-ischial diameter obtained by pushing the knuckles in between the tuberosities is moderately accurate, but, as I have indicated, the inter-tuber-ischial diameter may be quite adequate, and yet the rami may be so convex that the arch is functionally narrow.

(b) *Vaginal Examination*.—The fingers may be swept around the arch from one ischial tuberosity to the symphysis and on towards the other tuberosity, noting the path traced. If the patient is not perfectly relaxed the tonicities of the levatores ani interferes very seriously with this examination. Therefore, vaginal palpation is rather fallible, although a very good impression is attained in the anæsthetised patient when attempts are made to introduce the whole hand into the vagina, when the cramping constriction of the fingers by a narrow arch is readily recognised. I would like to record that I have always been able to get two fingers side by side into the apex of the arch, failure to do which is occasionally described as indication of narrowing.

(ii) *Distance between Ischial Spines*.—The ischial spines are easy to palpate on vaginal examination, and an attempt should be made to

assess their degree of prominence and of inversion into the pelvic cavity. If considerable, a suspicion of narrowing in this area must arise. Some idea of the actual diameter may be obtained by sweeping the fingers across the posterior vaginal fornix from one spine to the other.

#### CRITICAL SUMMARY OF AVAILABLE PROCEDURES FOR OUTLET MEASUREMENT

To summarise, I believe that X-rays offer a complete range of measurements, but that clinically, although various subjective impressions may be useful in experienced hands, the only reliable measurement is the antero-posterior diameter of the plane of least pelvic dimensions. In this country, the man-power situation in respect of radiographers hardly yet permits of routine X-rays, but it will be my endeavour to demonstrate that with the one clinical measurement of the antero-posterior diameter of the inferior strait of the pelvis it should be possible to pick out the dangerous cases for full radiological pelvimetry.

#### CRITERIA FOR DIAGNOSIS OF OUTLET CONTRACTION

It is difficult to define a precise criterion applicable to all cases. Williams (quoted Stander, 1946), for example, considered outlet contraction to exist in all cases where the inter-tuber-ischial diameter measured clinically was less than 8 centimetres, but he appears to have been pre-occupied with contraction in the coronal plane. In many centres the diagnosis of outlet contraction is made on the basis of Thoms' dictum (Stander, 1946) that where the sum of the inter-tuber-ischial and posterior sagittal diameters is less than 15 centimetres, the spontaneous delivery of a normal head is unlikely, pelvis which when measured radiologically or clinically fail to attain this standard of 15 centimetres being regarded as contracted at the outlet.

#### *X-ray Diagnosis of Outlet Contraction*

I believe it is possible with modern developments in radiological pelvimetry to be fairly precise. The diagnosis of contracted outlet may be made with complete confidence in any case where the X-ray measurements of the antero-posterior or of the transverse diameter of the plane of least pelvic dimensions is less than 9.3 centimetres. It is, of course, obviously correct that provided the disparity between the measurements be not too great, narrow measurements in one direction could be compensated for by an increase in the direction at right angles to it, if we assume further moulding of the head to be possible. So far as contraction below the plane of least pelvic dimensions is concerned, I suggest that the measurement which I have referred to as the corrected antero-posterior diameter of the outlet can be taken



as an index of outlet contraction. However, the critical figure in this respect is larger than 9·3 centimetres, for although the head may pass the plane of least pelvic dimensions well flexed, with its outline cylindrical and its diameter 9·3 centimetres, the classical mechanism of extension brings across the antero-posterior of the outlet an oblique measurement in the neighbourhood of 10 centimetres. I therefore hold that no matter what the actual size of the antero-posterior diameter of the plane of least pelvic dimensions, the outlet is to be regarded as contracted in any case where the corrected antero-posterior diameter is less than 10 centimetres. I admit that this whole system is based on rather theoretical arguments, but in my hands it has proved a rough but useful guide.

### *Clinical Diagnosis of Outlet Contraction*

I believe that firm diagnosis of outlet contraction can be made on clinical grounds in cases where the antero-posterior diameter of the plane of least pelvic dimensions is under 10 centimetres. This does not necessarily imply a contraction of the plane of least pelvic dimensions, but if the antero-posterior of this plane is less than 10 centimetres, the antero-posterior diameter of the outlet will certainly be inadequate at the time of extension of the head. On the other hand, from my studies in X-ray pelvimetry, I believe that if the antero-posterior diameter of the plane of least pelvic dimensions measure 11·5 centimetres or more, serious antero-posterior narrowing of the outlet can be ruled out, since even in the narrowest pubic arches the corrected antero-posterior outlet diameter very seldom differs by more than 1·5 centimetres from the antero-posterior diameter of the inferior pelvic strait. It will be noted that this figure of 11·5 centimetres is the same as the average figure given by Stander for this measurement.

The question then arises how far one is justified in assuming that an antero-posterior diameter of 11·5 centimetres for the inferior strait entirely rules out outlet contraction. Obviously this would be a rather dangerous assumption if it could be shown that serious reduction of the diameter between the ischial spines were likely to occur in association with such a large antero-posterior diameter. Whilst it is entirely possible that such reduction could occur, my own impression is that it is unlikely. Furthermore, it can be shown mathematically that an ellipse in which the long axis has a measurement of 11·5 centimetres will have an area greater than a 9·3 centimetre circle for all short axes greater than 7·7 centimetres, which would represent a very gross contraction of the diameter between the ischial spines, difficult to overlook on vaginal examination. I have no records of any such measurement less than 8 centimetres, while the smallest diameter recorded by Ince and Young (1940) in their survey is 7·5 centimetres. I therefore suggest that, whilst an antero-posterior diameter of 11·5 centimetres does not rule out the possibility of a contraction in the

least pelvic plane, it does indicate that severe insurmountable contraction in this area is very unlikely.

As a working rule, I suggest that in all cases in which the antero-posterior diameter from the lower border of the symphysis to the tip of the sacrum is 11·5 centimetres or over, outlet contraction is very unlikely unless the ischial spines appear to be particularly prominent and inverted; when this measurement is less than 11·5 centimetres, the pelvis should be regarded as suspect and referred for radiological examination; when the diameter is less than 10 centimetres, the outlet is definitely contracted.

### A CAUTION IN REGARD TO THE DIAGNOSTIC CRITERIA

In the foregoing examination of criteria upon which to class a pelvic outlet contracted, one's attention has been entirely focussed upon the average measurement of the foetal head when moulded in flexion. It is hardly necessary to emphasise that variations about the mean measurements are common, that partial or complete extension of the head can occur, and that accordingly outlet disproportion is possible in cases where the pelvic diameters are larger than the figures I have quoted. Disproportion may also arise in breech deliveries when, although the after-coming head may pass the pelvic brim in flexion, the fact that it is impossible to allow time for moulding may result in disaster if the outlet be at all narrow. In parenthesis, it should be noted how frequently the head of the baby delivered by the breech has a dolichocephalic shape. There is no cylinder here, but a disparity of measurements between the bi-parietal diameter and sub-occipito bregmatic diameter of a centimetre or more, with a sub-occipito frontal diameter which even in a 6 lb. baby may be as much as 11·5 centimetres.

Therefore, as in brim contraction, so at the outlet it is apparent that disproportion is more important than actual contraction, and that the breech is a particularly dangerous presentation.

A further point to be noted is that in the calculations which I have made I have deliberately chosen to ignore the soft tissues. There is no doubt that, in many of the cases diagnosed as contracted outlet after a stiff forceps, the major obstruction has been due to primigravid soft tissues. It is to exclude the possibility of mistaking faults in the soft passages for faults in the hard that I have deliberately neglected the soft tissues in making my calculations.

### LABOUR IN CONTRACTED OUTLET

If we assume a head of average size, of average consistence, and presenting in flexion, then outlet contraction may show itself in various ways. Its chief influence is during the second stage of labour, but it is not without effect upon the first and third stages, especially in those cases where the outlet contraction is an expression of a

generalised funnel tendency. The head then meets resistance from converging pelvic walls in the early portion of its descent, and there is a tendency to the development during the first stage of labour of uterine inertia, often wrongly labelled primary, and often associated with hour-glass spasm of the uterus, so justly feared as a cause of difficulty in the first and second stages of labour, and not infrequently a cause of disaster when it persists into the third stage.

Nevertheless, it is the terminal second stage which is characteristically obstructed by a contracted outlet. The effect upon the mechanism of labour at this point is too complex for analysis in a short paper of this type, but to summarise one may say that outlet contraction influences the mechanism of labour adversely by interference with the mutually interdependent functions of descent and of internal rotation of the head, not only by absolute narrowing but also by the alteration in the axis of the birth canal. It should be noted that the common incomplete rotation of the occiput to the front is not necessarily *per se* a cause of major dystocia, in contracted outlet.

### *Damage to Maternal Passages in Contracted Outlet*

(a) *Soft Passages*.—In association with the altered axis of descent, damage to perineum and posterior vaginal wall occurs frequently in association with a narrow pubic arch, which is the commonest cause of a complete perineal tear, especially in the case where the biparietal diameter is forced to emerge behind the tuberosities, when the soft tissues lack the protection given when this diameter is safely enclosed between the conjoint rami.

In antero-posterior shortening combined with or due to narrow arch, laceration of the lateral vaginal wall commonly occurs, often with very severe hæmorrhage, difficult to control. I have seen an apparently simple laceration at the lateral colpo-vulvar junction, partially overlapped and concealed by the labium minus, associated with wide separation of the lateral vaginal wall from the underlying tissues, with very serious paravaginal bleeding.

At other times one finds the major damage on the anterior vaginal wall, placed laterally. Unless bleeding occurs, lacerations in this area will usually escape notice, but they should be looked for in patients where one sees the vestibule with the tense and anæmic lower end of the vagina being rolled out of the vulva in advance of the descending head. I believe that waste space at the apex of the pubic arch is in some degree a protection against this form of trauma, with its sequela of stress incontinence of urine.

(b) *Bony Passages*.—Young (1940) has rightly pointed out that, with the softening of the pelvic joints normal in pregnancy, a delivery through narrow passages can spring the symphysis pubis with disastrous results to the sacro-iliac joints. From bitter clinical experience one is well aware how serious may be the results of a delivery through

a narrow outlet upon the patient's locomotion. A considerable legacy of crippling is left by many a forceps delivery, not forgetting coccygodynia, with or without fracture of the coccyx or the last piece of the sacrum.

### THE MANAGEMENT OF OUTLET CONTRACTION

(a) *Ante-natal Planning*.—In ante-natal planning, a choice of three alternatives presents itself :—

- (i) To allow labour at term.
- (ii) To induce labour prematurely.
- (iii) To carry out elective Cæsarean section.

In cases in which the baby presents by the vertex, and the corrected antero-posterior of the outlet is 9 centimetres or more, the first alternative will generally be chosen. So far as induction of labour is concerned, I feel personally that it has little place, owing firstly to the difficulty (even with the use of X-rays) in estimating the size of the head in relation to the outlet, and secondly to the fact that the head of a premature baby is ill-fitted to withstand the trauma resulting from an induction carried out too late. Elective Cæsarean section obviously has a field, for example, in cases where the corrected antero-posterior of the outlet is less than 9 centimetres, in the elderly primigravida at term, in primigravid breech presentation, in the presence of an unusually large child with a hard head, and in the subject of heart disease with failure of compensation; while, in the absence of a living child, a history of one or more still-births may compel Cæsarean section. However, each case has to be argued on its own merits, taking into account not only pelvic measurements but also the factors of parity, age, relative fertility, psycho-somatic background, relative size of brim and outlet with presence or absence of disproportion at the brim, etc., etc.

(b) *Management of Labour*.—Vaginal delivery having been planned, the keynote of management should be conservatism without procrastination. The temptation to employ oxytocics in the face of uterine inertia must be most firmly resisted. My own tendency is to employ suitable analgesic drugs during the first and second stages of labour until the head either is showing or is easily palpable through the perineum. Once this stage is reached, I interfere rather earlier than in a case regarded as normal, especially if the pains are poor and decreasing. The procedure adopted involves first postural treatment, that is the adoption of an exaggerated lithotomy position in the hope that rotation of the innominate bones about the sacro-iliac joint will result in enlargement of the antero-posterior outlet diameter. This is followed in the primigravida (and occasionally in the parous patient) by the performance of a very deep episiotomy, which, in its turn, is succeeded by the application of forceps.

In contracted outlet I advocate a very strict cephalic application of the forceps, without attempts to correct incomplete rotation of the occiput. With a truly conservative management, it is unusual to encounter a genuine occipito-posterior position, though directly lateral positions are extremely common. Kielland's forceps are ideal in such cases, but, with the head well down, the Haig Ferguson instrument,

CASE 6.—(Fig. 16).



FIG. 16.

X-ray of damage to pubic symphysis resulting from difficult forceps outside hospital. Patient almost completely crippled with bilateral sacro-iliac and supra-pubic pain on walking and changes of posture.

despite its generous pelvic curve, is usually quite successfully applied to the sides of the head in any position. Milne Murray's forceps are awkward unless the traction rods are removed.

Delivery should be completed by traction, the precise axis most suitable being discovered in each case by trial and error. Forcible forceps rotation is unnecessary, the head generally rotating spontane-

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ously during traction. Occasionally it emerges permanently occipito-lateral, and still more infrequently rotation to bring the occiput directly or obliquely posterior occurs at the vulva. In my experience these are not the disasters to the soft tissues which they are usually imagined to be.

If moderate traction with the forceps fails to cause any advance, attention is given to the patient's posture, the knees being still further drawn up in an attempt to enlarge the available antero-posterior space. If no progress is made after this, a second episiotomy, utterly removing all soft tissue resistance, usually allows completion of the delivery. I have never resorted to pubiotomy, nor to symphysiotomy, nor to deliberate fracture of the lower sacrum. Craniotomy is a last resort and very seldom required.

Cæsarean section may sometimes be adopted during labour. It has a place in the true funnel pelvis, when its performance is more commonly indicated on account of faults in the powers, rather than true outlet disproportion. The lower segment operation is obligatory, and, since the head has entered the pelvic cavity, its upward dislodgment may be so difficult that digital pressure from the vagina by an assistant may be required. Morbidity is high after such procedures, but the risk has to be taken occasionally.

### SUMMARY

1. The shape and dimensions of the moulded foetal head are discussed.
2. The pelvic outlet is described briefly in relation to the foetal head.
3. Types of outlet contraction are discussed.
4. Methods of measuring the outlet in a dried pelvis, and in the living subject are examined critically.
5. A method of determining an antero-posterior diameter of the outlet corrected in respect of pubic arch obstruction is described.
6. Criteria for the diagnosis of contracted outlet are laid down.
7. The effects of outlet contraction on labour, and the clinical management of contracted outlet are very briefly examined.

### ACKNOWLEDGMENTS

It is impossible to read a paper on this subject without admitting one's indebtedness to the American authors who have dealt so fully with this subject, whilst one has been influenced personally most profoundly by the lucid writings of Professor Chasser Moir. It is a pleasure also to express gratitude to my colleagues Dr M. J. D. Noble, who is responsible for the construction of the illustrative models and to Miss I. R. West, M.S.R., who is radiographer to the Ayrshire Central Hospital.



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## THE CARE OF THE SMALL PREMATURE INFANT \*

By H. L. WALLACE, M.D., F.R.C.P.Ed.

ONE of the more encouraging signs in British Medicine to-day is the increasing interest and concern shown towards the new-born infant and the dangers which beset it, and the realisation that here exists a rich field for preventive medicine in its best and widest sense. In this connection any scheme which aims at preserving infant life and thus reducing infant and neonatal mortality must include, as one of its major considerations, the care of the premature infant. This is borne out by statistics from the large centres up and down the country which reveal that more than half the neonatal mortality rate (deaths per thousand in the first month) is accounted for by prematurity. For example, from 1943-46, in the Simpson Memorial Pavilion of the Edinburgh Royal Infirmary, 69.3 per cent. of all infant deaths occurred in premature infants.

The accepted definition of prematurity is based on the weight at birth regardless of the estimated period of gestation; any infant weighing  $5\frac{1}{2}$  lb. or less at birth being regarded as premature. Although the particular type of maternal complication giving rise to premature labour may influence the infant's chances of survival, whatever its weight, it may be taken as a general rule that the lower the birth weight, the higher the mortality, and thus it is the *small* premature baby which constitutes the most difficult problem of care and management. This is not the occasion to elaborate details of nursing care and management, but I shall endeavour to discuss certain general principles which I believe to be fundamental, in that their understanding and observance will help to reduce the wastage of life so wont to occur when the spark burns so feebly.

The first essential required of those who would preserve the life of the small premature infant is that they eschew a defeatist attitude and appreciate the fact that no matter how small and feeble the infant at birth, if its heart is beating, it is worth putting forward every effort to save it. And here it must be emphasised that from the moment the baby is born a problem of extreme urgency is created and time is all-important. Unlike the full-term, mature infant, the small premature baby cannot be put on one side to be attended to later. On the contrary, it will require immediate and continuous attention from birth if it is to survive.

In order to be able to apply the most effective methods of care and

\* A Honyman Gillespie Lecture delivered in the Royal Infirmary on 19th September 1946.

attention in such cases it is important to appreciate that there are certain fundamental problems which are peculiar to prematurity, and that a knowledge of these forms the basis of our attempts to anticipate difficulties and to deal with them when they arise. I shall, therefore, outline each of these problems in turn and suggest methods which may be employed to meet them.

### THE PROBLEM OF BODY TEMPERATURE

Inability to maintain body heat is one of the fundamental weaknesses of the small premature infant, resulting probably from three main causes, namely, incomplete development of the heat-regulating centre in the medulla, low metabolic rate and relatively large skin area allowing of rapid heat loss. There are various other factors such as the feeble circulation, muscular inactivity, in fact, a generally lowered vitality.

To combat this state of affairs steps must be taken to conserve and maintain body heat whenever the infant is born, and any delay to adopt measures to this end may entail the loss of a life which otherwise might have been saved. Immediately after birth the infant should be wrapped in a warmed blanket and placed in a cot heated by well-insulated hot bottles or an electric pad. This will help to tide it over the immediate emergency, but with the minimum of delay it should be transferred to a suitably conditioned atmosphere where skilled and undivided attention is available. The provision of the correct atmospheric conditions is of great importance in the rearing of the small premature infant, and outside of an institution such ideal conditions are difficult to achieve. There are three requisites: the atmosphere must be warm, it must be humid, and it must be kept constant. It is only thus that sudden and dangerous variations in body temperature will be avoided. The actual temperature required will, of course, vary according to the degree of prematurity, the more premature the infant the higher the temperature needed to conserve body heat. For the small infant weighing less than 4 lb. the temperature of the room should be maintained at not less than 85° F. with the minimum of variation. Of almost equal importance to the temperature is the humidity of the atmosphere, since it is by maintaining a moisture-laden environment that evaporation from the skin and consequent heat loss is reduced to a minimum. Thus, a relative humidity of 65 to 70 per cent. should obtain in the premature nursery, and some ingenuity may be required to attain this standard in the absence of special air-conditioning plant. In a small room one or more steam kettles kept boiling day and night are a useful means of moistening the atmosphere. The methods of achieving the best atmospheric conditions must vary according to the facilities available in any given case, but it is essential always to bear in mind that, whatever the circumstances, mere heat is not sufficient, the ideal to be aimed at being humid heat. Constancy of temperature and humidity throughout

the twenty-four hours is also of great importance, and to attain this will require unceasing vigilance on the part of those in attendance.

Proper conditioning of the atmosphere is essential for maintaining body temperature and preventing heat loss, but in the feeble premature infant the metabolic rate is low and the administration of small doses of thyroid extract may serve as a stimulant of heat-production during the early critical days. Although the giving of thyroid is widely advocated in such cases, I must confess that my own experience with it has been disappointing and rarely have I noted any improvement which could be attributed to it. A suitable daily dose is gr.  $\frac{1}{10}$  per lb. of body weight.

### THE PROBLEM OF RESPIRATION

Some defect in the respiratory mechanism may be regarded as a constant feature in the small premature infant, calling for prompt action after birth if fatal asphyxia is to be averted. Various factors account for this defect, such as incomplete development of the respiratory centre and of the lungs themselves, and general weakness affecting the diaphragm and other muscles of respiration. Moreover, some degree of atelectasis is an invariable accompaniment of extreme prematurity.

Immediately after delivery any mucus which may be lurking in the upper respiratory passages should be gently but thoroughly sucked out through a soft rubber catheter inserted through the mouth into the pharynx. To avoid delay this procedure may be carried out by an attendant at the same time as the cord is being ligatured and divided, and then the infant is transferred immediately to the specially prepared cot. In very small infants the more heroic means of artificial respiration may prove harmful and are best avoided. The prompt clearing of the upper air passages, whilst of great importance, is only the first step towards establishing respiration and it is necessary usually to employ further measures of stimulation otherwise death from respiratory failure may occur. The most effective means of counteracting early asphyxia is the administration of oxygen with 5 per cent. carbon dioxide. The method favoured here is to cover the infant with a small improvised "tent" constructed out of old X-ray film and adhesive tape. This somewhat primitive contraption has definite advantages. It is inexpensive and easily and quickly made. Furthermore, it can be "made to measure," according to the size of the infant, and it is completely transparent, allowing of an uninterrupted view by the nurse in attendance. Such a tent cannot, of course, be hermetically sealed and this entails a certain wastage of gas. This method of administering oxygen and carbon dioxide is, in my opinion, to be preferred to the use of a mask or nasal catheter, both of which involve bringing a foreign body into direct contact with the infant. As regards the indications for the administration of oxygen and carbon

dioxide, I would like to urge that all premature infants weighing less than  $3\frac{1}{2}$  lb. at birth be given continuous oxygen and carbon dioxide for the first twenty-four hours and for longer if necessary. At the upper end of the weight scale this procedure may not be essential, but it is certainly a wise precaution to be carried out whenever possible, whereas in the case of the very small infant it should be regarded as an absolute necessity. In the latter case oxygen and carbon dioxide will probably be required for more than twenty-four hours after birth, and it is advisable to have supplies available for several days. After considerable trial we have found that the best results are obtained from continuous administration of the gas during the first twenty-four to ninety-six hours, depending on the condition of the infant, thereafter the tent may be removed for increasing periods providing no signs of asphyxia are evident. In the larger and less feeble infant occasional crying should be encouraged as an excellent respiratory exercise. This may be harmlessly initiated by flicking the soles of the feet with the fingers.

#### THE PROBLEM OF IMMOBILITY

It is important to bear in mind that the feeble premature infant is relatively immobile, and that this constitutes a danger. The extreme feebleness of all muscular movement has a direct effect on respiration, circulation and heat-production, and great care must be taken to ensure that nothing is done which might in any way impede the smallest muscular activity. To this end the question of clothing requires careful consideration, since there can be little doubt that there is still an unfortunate tendency to overwhelm the premature infant with swaddling clothes in the belief that only thus can it be kept warm. In actual fact, this is a custom strenuously to be avoided, since any material, however light, wrapped round the infant's body may be sufficient to embarrass seriously respiratory movement and to restrict altogether the feeble muscular contractions of the limbs which are so important to encourage. To allow of complete freedom of movement our practice is to dispense with clothing altogether in the premature nursery, the infant lying in its cot completely uncovered. This regime has proved highly satisfactory and has facilitated nursing, in that it allows frequent inspection of the whole body without handling. The infant lying thus, unrestricted, is free to exercise its limbs and to make the maximum use of its respiratory muscles, and it is surprising how, under such circumstances, even the smallest infant will kick and stretch and change its position unaided. With this regime of nudity, it is, of course, essential to maintain adequate atmospheric temperature and humidity, and to prevent chilling. In addition to encouraging spontaneous movements of the limbs and thorax, it is desirable also to change the infant's position from time to time to ensure that both lungs are given freedom to expand.

## THE PROBLEM OF BIRTH INJURY

It is well recognised that the premature infant is more prone to intra-cranial hæmorrhage than is the mature infant. The underlying defects which account for this are to be found in the skull, the blood and the blood vessels themselves. The skull of the small premature infant is soft and poorly ossified and may thus be over-compressed during labour. Owing to the very inadequate storage of vitamin K associated with prematurity the blood is more deficient in prothrombin than is the case in the mature infant, with the result that extensive and prolonged bleeding may occur after very slight trauma. The intra-cranial vessels are unduly fragile and tend to rupture easily thus providing a further risk of cerebral hæmorrhage.

The prevention of intra-cranial birth-injury is mainly an obstetrical problem, but in addition to obstetrical care the raising of the prothrombin level in the blood by the administration of vitamin K is desirable in all premature births. Although it is open to some doubt as to whether this precaution has any action in preventing cerebral hæmorrhage, it may serve to control and limit its extent by shortening the bleeding-time and thus promoting clotting. As a double safeguard in premature labour it is recommended that vitamin K be administered both to the mother during labour and to the infant within a few hours of birth.

## THE PROBLEM OF INFECTION

The new-born, mature infant has little natural immunity to infective organisms and the premature infant has even less. Thus the latter is extremely vulnerable to infection which may rapidly become septicæmic due to inability to localise the initial lesion. Neonatal infection in the premature infant carries a high mortality and is one of the main causes of death. In the Simpson Memorial Pavilion during the period 1943-46, 25 per cent. of all neonatal deaths amongst premature infants were due to infection. This sombre fact has serious implications in that neonatal infection is largely preventable, and when it does occur is usually indicative of faulty or careless technique in management. It cannot be over-emphasised that the thoughtless adult with some trivial infection may readily convey this to the small premature infant in a form which proves rapidly fatal. Brief reference to certain of the commoner infections of prematurity may serve to illustrate the importance of the preventive aspect of the problem.

The skin of the premature infant is delicate and abrasions occur easily, opening the way to infection. Thus the minimum of handling is desirable, combined with the utmost gentleness, and clean hands. It is advisable to dispense with bathing altogether, nor is it necessary to anoint the skin with oil. The only exception to this is the buttocks area, which may be gently cleansed with soap and water and cotton wool. This regime of inattention to the skin and of leaving it uncovered

has proved entirely satisfactory and skin infection has been a great rarity.

Oral thrush is not uncommon in the premature infant, especially if bottle-fed. Whilst most examples of this infection give rise to little anxiety and respond rapidly to treatment, a small proportion prove resistant and in these there is a danger of the infection spreading down into the œsophagus and even involving the stomach with disastrous results. Neonatal thrush results usually from some imperfection in nursing technique, although the infant may be infected at birth if the mother suffers from vaginal thrush. It is probable, however, that in the vast majority of cases infection occurs after birth and is thus largely preventable. It is not necessary here to discuss details of preventive technique such as cleanliness of hands, adequate sterilisation of bottles and teats, etc., but I would remind you of a fact which is sometimes forgotten, and for which the remedy is obvious, that an infant with oral thrush passes spores in its stools which are capable of causing repeated re-infection or of infecting other infants in the vicinity. One other point which is perhaps worthy of mention is the question of oral hygiene, since the practice still persists of swabbing the mouth of the new-born infant at regular intervals to keep it clean. In the case of the small premature infant this procedure is not only unnecessary but harmful, since the buccal mucosa is, like the skin, extremely delicate and easily injured and is thus liable to be rendered susceptible to infection.

Neonatal respiratory infection is of serious import in the premature infant and every effort should be made to prevent this occurring. Here again the infant may become infected through contact with a thoughtless attendant suffering from coryza or some other trivial upper respiratory condition, and it cannot be urged too strongly that all such individuals be rigidly excluded from the premature room. Sterile masks covering mouth and nose should be worn by all who have to come into close contact with the infant and, so far as possible, they should avoid breathing directly on to the infant's face. Pneumonia is one of the most serious of all infections which may attack the premature infant and is responsible for a high mortality. Added to the infant's low powers of resistance to any invading organisms, there is, in the case of pneumonia, the additional complication of atelectasis associated with prematurity. As mentioned previously, a recent survey revealed that 25 per cent. of neonatal deaths amongst premature infants in this hospital were due to infection. In no less than 20 per cent. of these the infection proved to be in the lungs. So great is the danger of neonatal pneumonia in the premature infant, and so liable is it to occur unsuspected in the early days, that recently we have commenced the routine administration of penicillin for the first seven days of life to all infants weighing  $3\frac{1}{2}$  lb. or less at birth. The penicillin is given orally in a dose of 6000 units every three hours and does not cause any ill-effects. It is as yet too early to state whether

this has any prophylactic value. These are but a few examples of common neonatal infection, but may I conclude this section with the reminder that all infection associated with prematurity is potentially dangerous to life, and yet nearly all is preventable. The remedy lies with us.

### THE PROBLEM OF FEEDING

In considering the feeding of the small premature infant we are at once confronted with two difficulties which may be termed mechanical and digestive. Such difficulties are peculiar to prematurity and create a situation which is quite different and much more complex than that which exists with the mature, full-term infant.

The mechanical difficulties are two-fold and require special emphasis because, if ignored, they may endanger life. The swallowing reflex in the feeble, premature infant is poorly developed and in fact, may be absent. Thus, if fluid is placed in the mouth it is liable to be inhaled into the air passages instead of being swallowed, with resulting fatal asphyxia. Also, on account of its general feebleness, the infant may lack the necessary power to suck and be quite incapable of taking feeds in the normal way from breast or bottle. It will be obvious, therefore, that it is not only the type of feed which has to be decided upon, but also the mode in which the feed is to be administered. The safest and most satisfactory method of feeding the small feeble infant is by œsophageal tube, and it is suggested that this procedure be adopted as a routine for the first few days for infants weighing less than  $3\frac{1}{2}$  lb. at birth. Tube-feeding in such instances has several advantages. It is comparatively safe and easily carried out; it does not require any effort on the part of the infant and causes less disturbance than any other method of feeding; it reduces the risk of choking (which is a real one) due to absence of the swallowing reflex. The technique of tube-feeding is simple and, provided that proper care is taken, the risks are negligible. It is not necessary here to describe the technique of gavage in detail, but one or two points might be mentioned. A suitable tube is a size 4 English catheter which is passed by way of the mouth and not through the nose. The infant should be propped up in the sitting position whilst the tube is being passed and the feed given. When the tube is withdrawn at the end of the feed, this should be done slowly, and it should be firmly nipped to prevent fluid dropping into the air passages as the end of the tube passes over the larynx. The whole procedure in experienced hands need not occupy more than a few minutes and it does not seriously disturb the feeblest infant. Tube-feeding is certainly much to be preferred to the exhausting and often fruitless attempts which are made to coax a premature infant to swallow a few mouthfuls of fluid by other means. It is not possible to lay down any definite rule as to how long tube-feeding should be continued, since no two cases are exactly alike, but when it is decided to change the mode of feeding this should be done gradually, the infant's



reactions being carefully noted. Once the swallowing reflex is fully established it is usually possible to institute pipette or bottle feeding. If the infant is still too weak to suck then the milk will have to be dropped into the mouth by means of the fountain-pen filler type of pipette, whereas if there are signs that sucking movements are being attempted these should be encouraged by using a special feeder such as the "Belcroy." Once this stage has been reached it is usually a short step to normal bottle-feeding, although some time may elapse before the infant is sufficiently strong to be put to the breast.

The other aspect of the feeding problem is the digestive one, since in extreme prematurity the gastro-intestinal tract is imperfectly developed. The work of Levine and Gordon (1942) suggests that the defect lies more in the supporting musculature than in the secretory and absorptive powers of the stomach and intestines, consequently over-distension may readily occur. It is obvious, therefore, that every care must be taken to avoid straining the limited capacities of an immature digestive system, and in this connection the worst error is quantitative over-feeding.

The safest and most satisfactory of all foods for the premature infant is the natural one, breast milk. And here I would like to lay stress on one point in particular. Propaganda to encourage breast-feeding has sometimes appeared to over-emphasise the purely digestive advantages of human milk. Whilst, admittedly, these are important, there is another aspect of breast-feeding which possibly is of equal, if not greater, importance, particularly in the case of the premature infant, namely, the transference of antibodies from mother to infant by way of the colostrum and milk. To deny the small premature infant this natural protection against infection is a grave decision and one that most certainly should not be taken lightly. Perhaps more forceful emphasis to mothers of this point might carry greater appeal than our somewhat vague statements concerning digestibility. If breast milk is available then one of the major problems of feeding is solved, and no effort should be spared to obtain an adequate supply. Unfortunately, in a proportion of cases of premature birth the mother may not be in a state of health conducive to satisfactory lactation and under such circumstances surplus milk from another mother might be used, or milk obtained from a breast milk "bank," if such has been organised in the hospital or area. In the event of failure to procure breast milk from any source, unnatural or artificial feeding will have to be resorted to—at best a poor substitute for the infant's natural food. Before being given to a premature infant cow's milk must be modified with great care otherwise digestive upset may result. Cow's milk fat is apt to be tolerated badly as also is the protein unless reduced in quantity and rendered more digestible by modification; sugar is tolerated relatively well. The aim is, therefore, to give a feed which is low in fat and protein and containing a high percentage of sugar. A food which fulfils these requirements is sweetened condensed

milk, the approximate composition of which is: fat 10 per cent., protein 10 per cent., sugar 60 per cent. In our experience this milk, suitably diluted, has proved to be the most satisfactory substitute for breast milk in the feeding of small premature infants. It is recommended to commence with a dilution of 1 part of condensed milk to 12 parts of water and gradually to increase the strength to 1 in 8. Lower dilutions than this are not desirable. A further advantage of this food is that in the process of condensing, the protein is altered and rendered more amenable to gastric digestion. The same applies to the various brands of dried milk, where the protein is modified by the drying process. Condensed milks and dried milks are, in my opinion, to be preferred to fresh cow's milk in the early feeding of these small infants. They are safer, more digestible and much easier to prepare. As already mentioned, our preference is for sweetened condensed milk, but such a food is suitable only for a limited period, and whenever the infant's digestive powers have become properly established a change should be made to a more balanced dietetic formula.

Whilst considering the most suitable food for the small premature infant it is, perhaps, appropriate to refer to casein hydrolysate as an addition to the diet. It would seem logical that, to supply the needs for rapid growth, relatively large amounts of protein are desirable, if not essential, but hitherto the main obstacle to maintaining an adequate supply has been the premature infant's intolerance to ordinary milk protein, particularly the casein in cow's milk. It has thus been necessary in the case of infants on unnatural feeds to make good their caloric requirements with relatively large amounts of sugar, a not very satisfactory solution to the problem. Since the beginning of this year, in an endeavour to ensure a more adequate protein intake, a preparation of casein hydrolysate has been added to the diets of those premature infants which, of necessity, had to be reared on unnatural feeds. This type of protein, prepared from casein by hydrolysis, is, in fact, "predigested" protein and, as such, should be readily assimilated even by the feeble premature infant where unsplit protein may not be well tolerated. The hydrolysed casein has been given in a dose of 3.5 gm. per kilo of body weight in the twenty-four hours, and fed to the infant either by bottle or œsophageal tube, according to the way in which it is receiving its ordinary milk feeds. The reason for this addition to the diet of the small premature infant has not been an attempt to produce a rapid gain in weight, but merely to make good a deficiency by supplying extra protein in an easily assimilable form. After only a few months of trial it is as yet too early to produce sufficient evidence as to the effect of this feeding regime, but it may be said that the results so far have been encouraging. I believe it is a fair statement that, on theoretical grounds at any rate, the administration of extra protein to these infants is rational when their requirements for rapid growth are considered. Furthermore,

experience has satisfied us that protein in this form may be given to the smallest premature infant with impunity. In one instance transient abdominal distension occurred which subsided when the extra protein was discontinued, but this was the only case which showed any unfavourable reaction. To date, we have administered the casein hydrolysate only to infants on unnatural feeds, but it is interesting to note that in a recent paper by the Swedish workers Jorpes, Magnusson and Wretling (1946), good results are reported in a series of breast-fed, premature infants, as shown by increased gain in weight when casein hydrolysate was added to the breast milk. These interesting observations from Sweden, taken in conjunction with our own results, suggest that the addition of casein hydrolysate to the diet of all premature infants, be they breast-fed or bottle-fed, would be of benefit.

When considering the questions as to what quantity of food should be offered to the small premature infant and how frequently the feeds should be given, it is difficult to be dogmatic since each infant is so much a problem in itself. It is advisable to withhold milk feeds for the first twenty-four hours; thereafter, a regular feeding regime may be instituted commencing with very small amounts which are gradually increased, whilst a careful watch is kept for signs of over-feeding. And here I might, perhaps, warn you that the temptation to over-feed the premature infant is great, but must be resisted. The wise policy is to err on the side of under-feeding during the early weeks of life. After twenty-four hours, 1 drachm of breast milk per lb. of body weight per feed, is a reasonable amount, and by the end of the first week it is usually safe to increase to 2 drachms per lb. Thereafter, the size of each feed is increased very gradually by 1 drachm at a time so long as no signs of distress or digestive upset become apparent. The weight curve is a valuable guide to progress, the aim being to maintain a steady, gradual increase in weight. Any attempt to produce a rapid, spectacular gain in weight during the first month should be avoided, since it is during this critical period that the risks of over-feeding are greatest. It is, I believe, a dangerous fallacy to expect the premature infant to gain weight more rapidly than the mature infant because it has "so much to make up." On the contrary, the most successful long-term results have been obtained in those cases where the average weekly gain in the first month has been considerably less than what would be expected in the normal, mature infant.

There is considerable divergence of opinion as to how often the small premature infant should be fed in twenty-four hours, but I would suggest that the tendency is in the direction of too frequent feeding. The argument in favour of the hourly or two-hourly regimes is to the effect that, since it is safe to give only a very small quantity at each feed, this must be given at short intervals if the total intake for twenty-four hours is to be adequate. In our experience, such

frequency of feeding has proved neither advantageous nor desirable, since it involves constant handling and disturbance of the infant, with all the risks which this entails, and it does not allow of proper alimentary rest between feeds. For all premature infants, including the smallest, a three-hourly feeding regime throughout the twenty-four hours has been the most satisfactory, eight feeds being necessary until the infant achieves a weight of 5 lb., when one of the night feeds may be omitted. Since the total quantity of milk given in twenty-four hours on this plan is slightly less than with more frequent feeding, gain in weight may be a little slower, but it is felt that this is more than compensated for by the reduced risks to the infant of infection and exhaustion and by the almost complete freedom from gastrointestinal upset.

### THE PROBLEM OF MINERAL DEFICIENCY

During pregnancy the foetal liver stores up a reserve of iron which may be drawn upon after birth to compensate for any deficiency of iron in the infant's diet. If pregnancy is interrupted, as in premature birth, this storage will be incomplete and, in consequence, a deficient reserve of iron is a constant feature in the small premature infant. The more premature the birth the greater the iron deficiency. Unless steps are taken to make good this deficiency a severe degree of hypochromic anæmia may develop in the later months of infancy and persist well into childhood. Whilst anæmia of this type is a normal occurrence during the early months of life—the so-called “physiological anæmia”—the premature infant has not the reserves of iron to restore the hæmoglobin level in later infancy, as usually occurs in the healthy, mature infant. To anticipate and prevent severe anæmia it is advisable to administer iron as a routine to all premature infants, commencing when they are one month old. The preparation which we have found to yield satisfactory results is ferrous sulphate, gr. 1, daily. This dose, which is well tolerated, appears to be adequate to raise and maintain the hæmoglobin level after its initial fall. It is probably advisable to continue the administration of ferrous sulphate until the infant is at least six months old.

In addition to iron shortage, the small premature infant has a deficient store of calcium and phosphorous at birth due to the fact that a high proportion of these minerals is acquired during the last two months of gestation. Thus, the soil is prepared for the development of rickets, and this tendency is further increased by the rapid rate of skeletal growth in the early months and by the fact that absorption of fat may be deficient. It is, therefore, essential to adopt preventive measures against rickets in all premature infants, whether they are breast-fed or bottle-fed, and the administration of vitamin D should be commenced at the end of the first month. The dosage requires to be larger than for the mature infant and it is recommended

that not less than 1200-1500 international units be given daily. These requirements may be fulfilled by giving 12-15 drops of one of the vitamin concentrates. It is necessary also to add vitamin C at this stage, this addition being specially important in bottle-fed infants owing to the negligible quantity of ascorbic acid in modified cow's milk. It sometimes happens that orange juice is not well tolerated by the premature infant and, if such be the case, two 25 mgm. tablets of ascorbic acid may be substituted.

In conclusion, may I offer the opinion that the small premature infant cannot receive the care and attention which is its due outside of an institution suitably staffed and equipped for the purpose. The ideal to strive for is an organized "premature service" whereby the premature infant may be safely and expeditiously transported from the home to such an institution with the minimum of delay, as with a surgical emergency. Only thus can we hope for any appreciable reduction in the present high death rate amongst these small infants.

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## COMMON PHYSICAL SIGNS IN OLD AGE

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THE significance of physical signs varies greatly according to the age of the patient. In youth, the presence of a harsh systolic murmur indicates the need to distinguish between possible congenital or rheumatic heart disease. In the aged, such a finding usually is of little or no importance. Loss of knee and ankle jerk in early middle age is usually a sign of serious organic disease of the nervous system, but over the age of seventy it is quite a common finding. The presence of dark brown pigmentation of the skin raises a possibility of Addison's disease in maturity; it becomes almost a physiological variant in senility. It is therefore proposed to mention briefly some of the physical signs encountered during a survey of 340 healthy Chelsea Pensioners, and to indicate their comparative frequency. The data thus gained have been fortified by experience gained as medical officer to the Royal Hospital, Chelsea, during five years of the war and by knowledge of the elderly gained both in general practice and a period of research in a "chronic" hospital.

### CARDIOVASCULAR SYSTEM

The commonest finding among healthy old people is a raised blood pressure. No less than 79 per cent. of the pensioners examined had systolic figures over 160 mm. Hg., and 25 per cent. had readings above 200 mm. The proportion of men with hypertension increased roughly according to age. The pulse pressure was usually high, being over 70 mm. in nearly all over seventy years of age. It varied between the 30-40 mm. usual in middle age to an extreme of 120 mm. in certain veterans. Experience has shown that high blood pressure is probably as common in old women as in old men.

As might be expected, arterial thickening is usual among the aged. Its degree, measured by palpation of the superficial arteries, increases with the age of the patient in most cases. There are, however, many exceptions; and relatively soft arteries at an advanced age are not unusual in women. Among the series of men examined, 15 per cent. did not show thickened vessels and 21 per cent. had marked tortuosity and calcification. The remainder showed varying degrees of thickening. For a more detailed description of the subject, a previous paper may be consulted (Howell, 1945).

In spite of the relative frequency of hypertension, clinical evidence of cardiac enlargement was not common. Only 6.5 per cent. presented

definite signs which were probably masked by fat or emphysema in other pensioners. But it is often found that an X-ray of the chest in old people with a raised blood pressure does not reveal a large heart. The pulse rate varies considerably in apparently healthy senescence, ranging from 45 per minute in a man with probable heart-block to 120 per minute in an ambulant pensioner with auricular fibrillation. Rates found in cases without any abnormal physical signs varied from 50 to 100 per minute. Arrhythmias were few, only 4 per cent. in the series recorded, and comprised extra-systoles, auricular fibrillation and heart-block. Sinus arrhythmia seems rare in old age, as does paroxysmal tachycardia.

Auscultation of the heart revealed murmurs present in 8 per cent. of pensioners. Three-quarters of these were systolic in timing, apical bruits being twice as common as basal ones, in both systolic and diastolic varieties. Less than 1 per cent. had double murmurs, either apical or basal. Since none of the men had a past history of rheumatic fever, and since syphilitic heart disease rarely allows survival over the age of sixty, most of these murmurs were probably sclerotic in origin. In a few men the aortic second sound was accentuated, but a loud pulmonary second sound was never heard among any of those examined. A summary of the abnormal cardiac findings will be found in the Table below.

TABLE  
*Cardiovascular Signs*

Hypertension . . . . .	79 per cent.
Hypertension over 200 mm. . . . .	25 "
Soft arteries . . . . .	15 "
Tortuous and calcified vessels . . . . .	21 "
Clinically enlarged heart . . . . .	6.5 "
Arrhythmias . . . . .	4 "
Systolic murmurs . . . . .	6 "
Diastolic murmurs . . . . .	2 "
Apical murmurs . . . . .	6 "
Basal murmurs . . . . .	2 "

### CENTRAL NERVOUS SYSTEM

Since only active and able-bodied pensioners were included in this series, the number of neurological lesions was small, only 5 per cent. Most of these were in men showing the sequelæ of past cerebral thrombosis, such as some degree of hemiplegia or aphasia. A few showed parkinsonism, but the total number of all lesions combined was only eighteen. Subsequently, however, a more detailed neurological survey was begun, using the same men as experimental material. Although this is not yet completed, it has given some indication of the findings likely to be encountered among the aged.

The most common physical sign found on neurological examination of Chelsea pensioners is absence of deep reflexes. It is unusual for

all to be either absent or present. The triceps and the ankle jerk are most often missing, the biceps, supinator and knee jerk less frequently. The reaction of pupils to light may be absent or else very slow. Reaction to accommodation is relatively rare in the older age groups. Among superficial reflexes, the abdominals are also often absent or difficult to elicit. Nevertheless, muscular tone is usually normal and power is often surprisingly good in these old men. Among signs of sensory impairment, partial or complete loss of vibration sense is very common. Joint position sense, however, is usually well preserved. A few men show diminution of pain sensation on the shins or forearms, and find some difficulty in temperature discrimination. The nose-touching test sometimes reveals a little dysmetria, but no cerebellar signs have yet been seen. Senile parkinsonism is, of course, encountered from time to time. As may be seen from these findings, it is easy to suspect *tabes dorsalis* on clinical grounds among the elderly—usually wrongly.

### LUNGS

Moist râles, rhonchi or sibili are not unusual in the elderly and were found in 10 per cent. of the pensioners examined. Only 5 per cent. of the cases had chests suggestive of emphysema. The presence of small dilated venules along the costal margins was not unusual, and a number of men had prominent veins which coursed over the chest wall. Only 1 per cent. of the pensioners had clubbed fingers due to chronic lung disease. Experience at the Royal Hospital and elsewhere has endorsed the dictum of Dr Samuel Gee who remarked that profuse expectoration may be present despite the absence of physical signs in the lungs.

### ABDOMEN

The most striking fact in the whole series was the finding of an enlarged liver in 37 per cent. of the pensioners examined. The size of the organ varied from being just palpable to reaching the umbilicus. Such hepatomegaly is unusual in others than former regular soldiers. It is therefore probably associated with conditions of their past military service. Two possible factors are past tropical disease, notably amoebic hepatitis, and alcoholic cirrhosis. No case of a healthy man with a palpable spleen was encountered.

A number of old people develop hernias late in life as their musculature becomes inefficient. Unfortunately no record was kept of the number of pensioners showing this abnormality until quite late in the survey, when twenty-five cases were noted. This figure of 8 per cent. is therefore inaccurate. As on the chest, it is quite common to find dilated veins on the abdominal wall, without any real prognostic significance.



## MUSCLES AND JOINTS

Some degree of fibrositis was present in 10 per cent. of the pensioners. This agreed with the figure of 14 per cent. who attended the Rheumatic Clinic for treatment in 1940. The commonest sites were the upper parts of the trapezius muscle, the lower parts of the deltoids, the lumbar muscles and the tensor fasciæ femoris. Osteo-arthritis was found in only 2 per cent. of the cases, but it must be remembered that men requiring treatment would be in the infirmary of the Hospital. Less than 1 per cent. showed evidence of gouty lesions.

## OTHER SIGNS

The skin of old people varies considerably in both colour and texture. Marked increase in pigmentation is quite common, ranging from a few brown or yellow spots on the trunk to a melanotic hue over a great part of the face and body. Ecchymoses are not infrequent, especially on the wrists and the back of the hands. Among the more feeble, incontinence of urine is often found. Some degree of deafness occurs in a proportion of old folk, and the difficulty of accommodating for near vision is well known. In the series under review, however, 21 per cent. of the men showed no abnormal physical signs whatsoever, and some 4 per cent. were noted as looking much younger than their actual age. Finally, it should be mentioned that the temperature in old age is definitely lower than the adult normal, figures of 96° F. and lower being not unusual in health. This will be discussed in detail elsewhere.

## SUMMARY

It has been found, therefore, that many physical signs are quite compatible with an active and healthy old age. A high blood pressure, cardiac murmurs, thickened arteries, absent tendon reflexes, some pigmentation of the skin and a lowered temperature are all to be found in normal old people. It is to be hoped that these few notes will prove of some assistance to those who have to evaluate the fitness of elderly persons from time to time.

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## NOTE

A QUARTERLY Meeting of the College was held on Tuesday, 4th February, the President, Dr D. M. Lyon, in the Chair.

Royal College of Physicians of Edinburgh Drs Henry James Parish (Petts Wood, Kent), Robert Carmichael Wood (Edinburgh) and John Alexander Malloch (Edinburgh) were introduced and took their seats as Fellows of the College.

Dr William Alexander Liston (Edinburgh) was elected a Fellow of the College.

Drs John Morton Henderson (Edinburgh), Nawab Ali (Bengal, India), Sujata Chaudhuri (Calcutta, India), Isidore Schrire (London), James Parlange Baird (Glenbuck, Ayrshire), Charles Groves (Edinburgh), William Hunter (Edinburgh), Jacob Du Toit (Pretoria, S.A.), Ralph Lulu Tobias (Cape Town, S.A.), Andrew Campbell Watt (Edinburgh), Hamidali Mahdubali Khan (Camp Poona, India), Roland William Riddell (London), Vera Sarah Emanuel (Johannesburg, S.A.), Cecil Harris (Troon, Ayrshire), Harland Cornelius Hastings (Edinburgh) and Alastair Robert Currie (Glasgow) were elected Members of the College.

## NEW BOOKS

*Tuberculosis and Chest Disease for Nurses.* By G. S. ERWIN, M.D. Pp. 231, with 39 illustrations. London: J. & A. Churchill, Ltd. 1946. Price 10s. 6d. net.

In this book an attempt has been made to provide a book suitable for all members of the nursing profession. To cater for three grades—student nurse, State-registered nurse, and sister tutor—is obviously difficult, and the book will prove heavy going for the first group. The problems of tuberculous infection and pulmonary tuberculosis are discussed in detail in 142 pages, and an account of non-pulmonary tuberculosis, too compressed to be really useful, occupies 27 pages. Sixty-two pages are devoted to respiratory diseases. Operative measures of treatment are presented in an interesting way, but many unexplained technicalities of expression are used which will confuse even well informed sister tutors. One feels that the experience of the author is cramped by the necessity of keeping the book within small volume, but its value would be increased by simplification of the subject matter and by an easier presentation of pathological details.

*Synopsis of Physiology.* By ROLLAND J. MAIN. Pp. 341, with 21 illustrations. London: Henry Kimpton. 1946. Price 18s.

This book has been written for the benefit of the senior student and the graduate and is essentially one on applied human physiology. In its small compass is contained a comprehensive fund of information, yet the presentation is not in the form of a succession of staccato sentences, a feature which so frequently detracts from synopses; it is, indeed, a very easy book to read. It is completely up to date, and graduates will be grateful to the author for this small book which presents the current state of knowledge in the all important basic subject of physiology, and links it to the problems with which they are continually confronted.

## NEW EDITION

*Sternal Puncture.* By A. PINEY and J. L. HAMILTON-PATERSON. Third Edition. Pp. xv+80, with 13 illustrations. London: William Heinemann. 1946. Price 15s. net.

This book gives a concise review of bone marrow puncture, most of the text being excellent. The points of difference between megaloblasts and normoblasts are not clearly brought out in the first chapter, and the chapter on Protozoal Disease is weak. The illustrations are fairly good, but those showing the marrow in pernicious anæmia could be improved. Generally speaking, however, this book should please those who desire an up-to-date summary of this useful method of investigation.

## BOOKS RECEIVED

- BAILEY, HAMILTON, F.R.C.S. (ENG.). *Pye's Surgical Handicraft*. Fifteenth Edition. (John Wright & Sons Ltd., Bristol) 25s. net.
- BERKELEY, COMYNS, Sir. *A Handbook of Midwifery*. (Cassell & Co., London) 12s. 6d. net.
- Brompton Hospital Reports. Volume XIV, 1946. (Gale & Polden Ltd., Aldershot) 10s. net.
- CHESTER, S. KEEPER, and DONALD G. ANDERSON. *Penicillin in the Treatment of Infections*. (Oxford University Press, London) 8s. 6d. net.
- DUKES, C. E., M.D., M.Sc., D.P.H. *Bacteria in Relation to Domestic Science*. (Oxford University Press, London) 12s. 6d. net.
- DUNCUM, BARBARA M. *The development of Inhalation Anæsthesia*. (Oxford University Press, London) 35s. net.
- Irish Medical Directory and Hospital Year Book, 1946-47. Ninth Edition. (The Parkside Press Ltd., Dublin) 15s. 6d.
- JOE, ALEXANDER, D.S.C., M.D. (ED.), F.R.C.P. (ED.), D.P.H., D.T.M. AND H. *The Acute Infectious Fevers*. (J. & A. Churchill Ltd., London) 18s.
- JORPES, J. ERIK, M.D. *Heparin in the Treatment of Thrombosis*. Second Edition. (Oxford University Press, London) 18s. net.
- LEE, ALFRED J., M.R.C.S. *A Synopsis of Anæsthesia*. (John Wright & Sons Ltd.) 12s. 6d. net.
- MACNULTY, Sir ARTHUR. *The Renaissance and its Influence on English Medicine, Surgery and Public Health*. (Christopher Johnson, London) 5s. net.
- MASTERS, DAVID. *Miracle Drug*. (Eyre & Spottiswoode Ltd., London) 10s. 6d. net.
- MINSKI, LOUIS, M.D., F.R.C.P. *A Practical Handbook of Psychiatry for Students and Nurses*. (William Heinemann, London) 6s. net.
- MONCRIEFF, ALAN, M.D., F.R.C.P., and THOMSON, WILLIAM A. R., M.D. *Child Health*. (Eyre & Spottiswoode Ltd., London) 14s. net.
- PATERSON, DONALD, M.D. (EDIN.), F.R.C.P., and MONCRIEFF, ALAN, M.D. (LOND.), F.R.C.P. *Diseases of Children*. Fourth Edition. (Edward Arnold & Co., London) 30s. net.
- SEQUEIRA, JAMES H., M.D. (LOND.), INGRAM, JOHN T., M.D. (LOND.), BRAIN, REGINALD T., M.D. (LOND.). *Diseases of the Skin*. Fifth Edition. (J. & A. Churchill Ltd., London) 63s.
- SHAW, WILFRED M. A., M.D. (CANTAB.), F.R.C.S. (ENG.), F.R.C.O.G. *Textbook of Midwifery*. Second Edition. (J. & A. Churchill, Ltd., London) 21s. net.
- TASSMAN, I. S., M.D. *The Eye Manifestation of Internal Diseases*. Second Edition. (Henry Kimpton, London) 50s. net.
- VAY, DAVID LE, M.S. (LOND.), F.R.C.S. (ENG.). *A Synopsis of Orthopædic Surgery*. (H. K. Lewis & Co. Ltd., London) 15s. net.

# Edinburgh Medical Journal

March 1947

## THE EVOLUTION, FUNCTION AND SCOPE OF THE MEDICAL SOCIETY \*

By EDWIN BRAMWELL, M.D., LL.D., F.R.C.P.Ed. and Lond.  
Professor of Clinical Medicine (retired)

WHEN you, Mr President, and your Council decided upon the subject for to-night's discussion, and invited me to present a paper with which to introduce it, you left it to me to choose the precise wording of the title. The theme you have selected—the function and scope of the Medical Society—should appeal to all of us for I understand that it was of this Society and its future you were particularly thinking. It is wise, is it not, to pause from time to time and take stock of our position? Since the activities of our Society were in abeyance during the years of war, this, the Inaugural meeting of a new session, is an opportune occasion upon which to ask ourselves how we stand and to discuss our future policy. Does the Society take the place it did? Are changes called for which might be beneficial? These are questions which demand an answer not only in the interests of the Society but in those of Medicine and the Edinburgh School.

Any hesitation I may have felt in accepting your invitation to present this paper was dispelled when, after writing these words, I re-read the valedictory address by our former wise and much beloved President, Logan Turner, who was steeped in the traditions of the Edinburgh School. Listen to his words when he addressed the Society in 1929. "The methods of conducting its business and its usefulness have been sometimes adversely criticised and animadverted upon. Does its vitality remain altogether unimpaired? . . . Does the Society still fulfil the function desired by its founders? Is it as attractive and satisfying as it ought to be? . . . Let me ask those who come after me to consider carefully how improvements might be effected and increased interest stimulated in the work of the Society."

So far as I am aware no serious attempt has been made to follow up and act upon this suggestion. The time is ripe, is it not, to consider the possibilities?

Since your remit allows of a wide interpretation I would ask you, by way of introduction, to look back with me into the distant past and

\* Read at a meeting of the Edinburgh Medico-Chirurgical Society on 6th November 1946.

visualise the beginnings of medical clubs and societies in former days of which we have no record. Medicine has always offered an extensive field for speculation and in early times, when little exact knowledge existed, there was even more room for difference of opinion than there is to-day. Authority for long was paramount. The learned exponents of the cult, the orthodox graduates of the schools, no doubt regarded with scorn views expressed by others which were at variance with the teaching of the recognised masters. But with the dawn of scientific medicine in the Middle Ages, the doctrines of the past handed down through the centuries by the writings of Galen and others were no longer regarded as sufficient and self-satisfying. Increasing attention was paid to accurate observation and correct inference; thus, little by little, true knowledge was accumulated. The enquiring mind of man in the search for truth will never rest content. Our forebears, meeting perchance in a tavern, would no doubt discuss the problems of the day and commend or criticise current views and the opinions of their colleagues. Little gatherings specially called for the purpose were the forerunners of the medical clubs and societies of to-day.

A brief reference to medical social clubs is called for in passing, since clubs of the kind do much to foster good-fellowship. Edinburgh has been noted for its numerous dining clubs. Two local medical dining clubs of long standing I would especially mention. The Æsculapian Club, founded by Andrew Duncan, Senior, in 1773, has twenty-two members, all Senior Fellows of one or other of our Royal Colleges. A purely social club, its members dine together every quarter as they did in Duncan's day. Professional rivalries and animosities, should they exist, are banished when the Æsculapians, all good fellows, meet around the festive board. Another time-honoured institution—the Edinburgh Harveian Society—was founded by Andrew Duncan, Senior, in 1782. The Harveians, as many of you know, meet annually in June, when the President for the year delivers the Harveian Oration. At the dinner which follows, the neophytes or new members are introduced and go through the ceremony of eating the heart; thereafter the President proposes the toast of the evening, "The Immortal Memory." "The threefold purpose envisaged by the founders of the Edinburgh Harveian Society," wrote H. L. Watson Wemyss in his charming little history, "were the commemoration of departed worth, the promotion of social intercourse among medical men and the stimulation of rising genius."

Nor shall I apologise if, before I speak of what may be called the learned societies, those concerned with the theory and practice of medicine, I make mention of the Students' Medical Societies. It is interesting to note that both in Edinburgh and Aberdeen the students were the first to establish medical societies, an example which was not followed by their seniors until a later period. Our Royal Medical Society, which was founded in 1737 and received its Royal Charter in 1778, the oldest medical society in this country, fulfils a most useful

function if the student avails himself of the opportunities it affords. Here he may perhaps acquire some facility in debate; he may learn something of the elements of committee work and procedure and, if called upon to read a dissertation, he may be initiated into the requirements called for in the composition of a scientific paper. And is it not true that the purpose of education should be "to train the mind rather than crowd the memory"? The Royal Medical Society with its handsome hall, its library and reading rooms, has traditions to which many of you, who in your day were active members, look back with pride. Sir Humphry Rolleston in his MacAlister Lecture, published in *The Annals of Medical History*, New York, 1930, paid homage to the Society when he wrote: "The Presidency of the Royal Medical Society in the Modern Athens frequently foretells eminence in later life; no one interested in medical history can have failed to have been struck by the frequency with which leaders in our profession have filled this office." I sometimes wonder whether nowadays the Society is utilising its meetings and fulfilling its functions to best advantage when so much time is devoted to listening to orations delivered by prominent members of the profession.

"The earliest British Medical Societies," writes Hingston Fox, "were instituted in the eighteenth century. They seem to have been small committees which collected papers on medical subjects for publication. Such was a Society at Edinburgh, of which Monro primus was evidently the soul, and which began in the year 1731 to compile yearly volumes of *Medical Essays and Observations*." "In this respect," writes Rolleston, "Edinburgh certainly set an example to England." This Society in 1783 became the Royal Society of Edinburgh. "Except for the *Philosophical Transactions of the Royal Society of London* there were not any periodicals in which medical communications could appear until in the eighteenth century medical clubs and societies arose and brought out the papers read before them. Medical journals followed, and apparently were a development of the publications of Medical Societies. . . . Before the birth of medical journals, the only means of publishing medical papers were books and pamphlets" (Rolleston).

Several small medical societies were set up in London and elsewhere during the later decades of the eighteenth century. John Fothergill, who had been an active member of the Students' Medical Society when an undergraduate in Edinburgh in 1734, was a moving spirit in instituting one of these. This Society of Physicians published six volumes of *Observations and Inquiries* between 1753 and 1784. Then in 1773, John Coakley Lettsom was responsible for the inauguration of the Medical Society of London. It is interesting to note that it was in the same year that Andrew Duncan founded our Æsculapian Dining Club and that Lettsom visited Edinburgh, though he was not an Edinburgh graduate, when he and Duncan must almost certainly have met. Lettsom was a friend and great admirer of Fothergill,

who had become one of the first physicians of the day, and in his will he left £500 to the Medical Society of London to endow a Medal in his memory.

The constitution and arrangements of the Medical Society of London are very similar to our own. Lettsom laid it down in his design that the Society should be "A Society of medical practitioners of various ranks who would meet together to compare their observations and compare mutually their thoughts, taking note of new discoveries at home and abroad." The Medical Society of London, as Sir St Clair Thomson pointed out in his Presidential Address to that Society in 1918, has always been very conservative. Meetings are held on a Monday twice a month; only males are admitted to the Fellowship of the Society or as visitors to its meetings; the annual subscription remains at one guinea a year; papers are not permitted to exceed what can be read in twenty minutes, and the copyright of papers read before the Society and accepted for publication becomes the property of the Society. Every Fellow receives a copy of each number of the *Transactions*, which first appeared in 1787 and later spasmodically until 1872, since when they have been published annually. Apart from a departure from the early laws whereby the President when in the Chair wore a cocked hat, a custom which persisted till 1832, there seems to have been little change in its regulations since the Society's inception. But the Society has had its vicissitudes. So long ago as 1805 a number of its Fellows, who disapproved of the re-election of the President, a Dr James Sims, an Edinburgh graduate by-the-way, who had occupied the Chair for twenty-two years, resigned and combined to form a new society—the Medical and Chirurgical Society. This new Society received a Royal Charter in 1850. When in 1907 the Royal Medical and Chirurgical Society persuaded various special societies to amalgamate with it and form the Royal Society of Medicine, the Medical Society of London, influenced no doubt by the possession of its convenient quarters in Chandos Street, its hall and valuable library, possibly too by some feeling of resentment, a relic of former antagonism, declined the invitation. "The Medical Society of London," writes Hingston Fox in 1919, "has maintained throughout its course a general outlook upon medical questions, endeavouring to view them from different sides, those of clinical experience, research and theory. For this purpose," he continues, "evidence is needed alike from the physician, the surgeon and the family man, whether in town or country. Such a comprehensive scope has provided a useful counterpoise to that undue specialism which has resulted from the increase of knowledge. . . . The Society is notable in medical history as probably the first to be constituted on what may be called a democratic basis, serving the interests of the medical profession as a whole."

Specialism is however a necessary consequence of the progressive extension of the field of medicine, and many specialist societies came

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<sup>1</sup> *B.M.J.* 1945, *ii*, 119.

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into being during the second half of the nineteenth century, their meetings made possible by the improved methods of transport. Specialism is essential for scientific advance but, as our President has pointed out in a thoughtful and stimulating paper on this subject in the *Edinburgh Medical Journal* of January 1941, disintegration has both its advantages and disadvantages. I shall, however, return to this subject later in discussing the effect of specialism upon the activities of our Society.

Attempts had been made from time to time to unite all the London Medical Societies in one body representative of every department of medicine and surgery, but it was Mr (afterwards Sir John) MacAlister who was eventually responsible for the inception and success of the Royal Society of Medicine. MacAlister, it may interest you to know, studied medicine in Edinburgh for three years (1875-78) but was obliged to give up because of ill health and did not graduate. He became a librarian, and in 1887 was appointed Resident Librarian to the Royal Medical and Chirurgical Society. It was in 1907 that that Society obtained a supplemental Royal Charter by which its name was changed to the Royal Society of Medicine. The new Society was empowered by its Charter to form sections and to admit Members of other Societies, which agreed to dissolve and amalgamate, to its Fellowship or to the Membership of its sections; no less than seventeen London Medical Societies were thus included. All registered medical practitioners are eligible as candidates for the Fellowship of the Royal Society of Medicine or to the Membership of the individual sections. The Society holds the copyright of any paper or description of a case accepted for publication and its Proceedings are circulated to the Fellows and Members. The Society's present house at 1 Wimpole Street with its lecture theatres, reading and writing rooms and library was opened in 1912.

Let me now direct your attention to our Society and ask you "to consider carefully," as Logan Turner asked us, "how improvements might be effected and increased interest stimulated in the work of the Society?"

The Medico-Chirurgical Society of Edinburgh was founded in 1821. It owed its inception to the vision and energy of three men—Dr John Gairdner, the father of Sir William Gairdner whom some of you may remember, Dr Robert Hamilton and Mr William Brown. The veteran Andrew Duncan, Senior, then seventy-seven years of age, was our first President. Logan Turner in his valedictory address gives a delightful picture of Edinburgh at that time and of some of its medical personalities "in this remarkable epoch in the history of our profession." The origin of the Society and its purpose are set out in the first volume of the *Transactions*, which was published in 1824, three years after its foundation. "It appeared"—I quote from the preface—"to many of the practitioners and teachers of Medicine in this city, that an association among themselves, similar to those which have conferred

so much benefit on medical science in London and Dublin, was very desirable for their own gratification and instruction. And from the number of medical men, in all parts of the world, who had been initiated into their profession in this university, it may be hoped that the Society may become the depository of much more varied and extensive observations, than the resident members themselves can hope to furnish. The expectations of the founders of the Society have been hitherto fully realised." Our constitution and arrangements are very similar to those of the Medical Society of London and to many other local medical societies which now exist throughout the country. According to a list of names and addresses of the Members of the Society, which is included in the first volume of the Society's *Transactions*, there were in 1824, 2 Honorary Members, 85 Ordinary Members or Members living in Edinburgh, and 107 Corresponding Members or Members living in other parts of Scotland, in England or overseas. Then as now the Office-Bearers consisted of a President, 3 Vice-Presidents, 2 Secretaries, a Treasurer, and 8 other Members of the Council. It is not without historic interest to note that the letters F.R.S.E. appear after the names of ten of the fifteen Members of the Council, but that there is nothing to signify which of the Members of the Society were Fellows of one or other of our two Royal Colleges. I shall not, however, attempt to trace the history of the Society this evening for that topic, though replete with attractive incident, would be a diversion which does not serve my present purpose.

The educative value of our Society is stressed by its founders. This is a most important, perhaps the most important, function of a medical society. I would quote some remarks from an address by Sir William Osler on the "Educational Value of a Medical Society" for his words, although delivered forty-three years ago, are generally applicable to the conditions of to-day:—"The killing vice of the young doctor," he writes, "is intellectual laziness. . . . There is no greater test of a man's strength than to make his mark in 'the stand and wait years.' . . . Now here is where the medical society may step in and prove his salvation. . . . It keeps his mind open and receptive and counteracts that tendency to premature senility which is apt to overtake a man who lives in a routine. . . . In a city association the demonstration of instructive specimens should form a special feature of the work. . . . The new pathology, so fascinating and so time absorbing, tends I fear to grow away from the old morbid anatomy which is of such incalculable advantage to the physician. . . . Of still greater advantage is the clinical side of the Society. No meeting should be arranged without the presentation of patients, particularly those illustrating rare and unusual forms of disease. . . . Perhaps given over wholly to commercialism, a doctor feels it a waste of time to join a Society. . . . The man who knows it all and gets nothing from the Society reminds one of that little dried-up miniature of humanity, the prematurely senile foetus whose tabetic marasmus has added old

age to infancy. He feels better at home, and perhaps that is the best place for a man who has reached this stage of intellectual stagnation. . . . The times have changed and are changing rapidly, but the ideals which inspired them (here the writer is speaking of the founders of the Society he is addressing) are ideals which are ever old and yet always fresh and new."

The words of Sir William Osler are, I repeat, as applicable to-day to a medical society composed largely of general practitioners as when they were written. But conditions have changed and continue to change for the progressive development of specialism and the setting up of specialist societies have had their effect upon our Society in which the specialists have become increasingly more numerous and, so our Treasurer, Mr Carlow, informs me, now predominate. There is, this at least is my impression, a lack of enthusiasm and interest in and a *laissez-faire* attitude towards this Society which did not exist when I was admitted to its membership. The development of specialism has undoubtedly been responsible for the creation of this atmosphere.

That our present arrangements are not regarded as altogether satisfactory by the general practitioner is evidenced by the setting up of the Clinical Club some years ago. The general practitioner may have felt that the formality of our procedure and the lengthy technical papers often included in our billet did not meet his needs. The very name of the new Club suggests, does it not, that our Society is not, in his opinion, sufficiently clinical in its outlook? The general practitioner wishes information more particularly as to the use and relative value of new methods and the feasibility of their application to the problems of diagnosis and treatment which he personally encounters. Our Society should, I think, have foreseen this defect and provided for it. Nor do our arrangements satisfactorily meet the need of the specialists among whom the physicians and surgeons constitute a large proportion. The surgeons cannot be expected to attend a meeting at which the sole item of business is, as sometimes happens, a lengthy paper of purely medical interest, nor does a technical surgical communication appeal to the physician. Yet the meetings of a medical society may be of the greatest educative value to the specialist.

There is a danger, is there not, should we pursue our present policy, that we fall between two stools, if we have not already done so? Has not the time come when we should very seriously consider whether, and if so in what way, we can satisfy the requirements of *both* the specialist and the family practitioner? This is the question which I wish to put before you this evening.

Some of you may say, why should we not continue as at present for does not the Medical Society of London continue to flourish and its constitution and arrangements are very similar to our own? But the circumstances are very different, for the Medical Society of

London has its centrally situated buildings, its hall and library, all sources of attraction. One must remember, too, that that Society has the whole London area from which to draw its members, and that many of its members who are specialists are also Fellows, and attend the Sectional Meetings of the Royal Society of Medicine.

Again, it may be argued that it is unnecessary for us to make any arrangements for the specialists since they are provided for by the Royal Society of Medicine, the Associations of Physicians and Surgeons and other special societies, while there are numerous journals in which they can publish their communications. But it is not possible for the specialist living in Edinburgh to attend meetings regularly which are held in London, nor is it possible for all to attend the annual gatherings of other specialist associations or societies, even if they happen to be members, since these may meet during the teaching term and at a considerable distance.

There is, too, another aspect of this question of specialism which I wish particularly to emphasise. Of recent years there has been an increasing tendency to what I may, for convenience sake, designate as sub-specialism, both in Medicine and Surgery. The field of Medicine—and this applies also to Surgery—is now so wide that it is no longer possible for the physician, even though he may be a satisfactory and successful general consultant, to pose as an acknowledged authority in all its departments. The physician of to-day if he is to make a reputation and be recognised by his colleagues as an expert must concentrate upon a restricted area. But, if he succeeds, his time may be so much occupied in dealing with the specialised type of clinical material submitted to him and in keeping abreast of the literature of his sub-specialty that he may find it difficult to maintain as intimate a knowledge of other branches as he would like. We in Edinburgh who are engaged in teaching both undergraduates and graduates, while we may be specialists, cannot be exclusivists. The physician in charge of wards, with his assistant physician and clinical tutor, lives in a kingdom of his own and may know little of the work of his colleagues and as to what is happening in other medical units in the hospital. Would it not be greatly to the advantage of the physicians and their assistants—the same applies to the surgeons—if they had opportunities to meet and share their knowledge and experience? I know full well that I personally would have heartily welcomed and benefited from such meetings at which one could listen to communications or to résumés of recent advances by my colleagues based upon their special experience and knowledge. But further, such meetings, quite apart from their educative value, would supply what was, and I believe still is, a defect in our Society for they would encourage the younger specialist by affording him an opportunity to present his work and show his prowess.

I shall now put before you certain suggestions for your consideration which, in my opinion, would serve to meet the educative requirements

of both the specialist and general practitioner, would stimulate the output of original communications and would thereby emphasise the individuality and enhance the reputation of the Medical Society of Edinburgh. My suggestions are :—

(1) That in place of our present arrangements we institute a Medical and a Surgical section ; that we invite the Clinical Club to join us as a third section of the Society—with an appropriate title to be decided upon and with its own arrangements especially adapted to the requirements of the general practitioner—and that we approach the Obstetrical Society and ascertain whether they will be willing to amalgamate with us as a fourth, an Obstetrical, section.

(2) That each section should have its Chairman and Secretary—men selected for their enthusiasm, energy and interest in the Society and the welfare of the Edinburgh School, for the success of such a scheme will depend largely on the activity of the sectional office-bearers—and that the Chairmen of the sections be *ex-officio* Members of the Council and co-operate with the Editor of the *Transactions* in the selection of communications for publication.

(3) That each section should meet once a month though conjoint meetings of two or more sections be arranged when subjects of common interest arise.

It would be desirable, I think, in the first instance at any rate, that we limit the number of sections to the three or four which I have mentioned, but I would suggest that the ophthalmologist, the ear, nose and throat expert, and other specialists be invited by the individual sections to present communications or to open or take part in discussions from time to time on borderland subjects. This would help to counteract the danger of disintegration which, as you, Mr President, have pointed out, is apt to result in the narrow outlook of exclusivism.

Some of you may express doubts as to whether the sections would obtain a satisfactory attendance if each section were to meet once a month. But is it not the case that, as it is, this Society, the Clinical Club and the Obstetrical Society hold their meetings monthly ? The success of the medical and surgical sections, which should be open to all members of the Society, will depend largely upon the enthusiasm with which these suggestions are received and carried into effect by the junior physicians and surgeons, the Chiefs of the future. I hope, however, that the proposed changes will meet with the whole-hearted approval and co-operation of the seniors. Should any feel—this I imagine is most unlikely—that they would derive little personal benefit from the meetings of their respective sections, they should remember that they have here an opportunity to stimulate and educate their colleagues. There is, I may remind you, good reason to believe that in the years to come we shall have numbers of graduates studying in Edinburgh who are specialising in Medicine, Surgery, and it may be Gynæcology and other specialities. These graduates should be admitted

to the Society as temporary members ; they would, I am sure, appreciate this privilege and their presence would give an added zest to the proceedings.

Doubts may be expressed as to the possibility of obtaining the necessary business for the medical and surgical sections if each section meets once a month. My personal opinion is that there should be no such difficulty for, in addition to original papers and pre-arranged discussions, short preliminary communications on material which has not yet appeared in print, and authors' abstracts, by members of the Society, of lengthy papers which they have recently published, would I think be appreciated. Occasional résumés of recent advances by those who are conversant with the literature of their respective specialities, might also constitute an additional feature of these sectional meetings. I, in my day, would have been only too pleased to have had the responsibility of acting as secretary to a medical section such as is here proposed. Clinical meetings—meetings devoted to the demonstration of clinical cases—were an item of our business which was much appreciated. But I understand that last session the first of our two clinical meetings had to be abandoned since only one reply was received in response to nearly a hundred intimations sent out with invitations to show cases, and that only twelve members attended the second meeting which was held at Bangour. This is a very different state of affairs to that which existed some years ago. What is the reason ? Are the clinicians so busy that they have not the time ? Are they engrossed or obsessed with the methods of the laboratory to the detriment of the attention formerly paid to direct observation and the study of the individual case ? It cannot be that the clinicians have no cases of interest under their care. Is apathy the explanation ? Clinical meetings may be as attractive and educative as ever they were. They must be resuscitated. Should not the clinicians, who have material of interest, regard it as a duty to give the Society the benefit of their experience ?

Finally, I would say something of the *Transactions*, though I approach this subject with some diffidence. Since 1922 our *Transactions* and those of the Obstetrical Society have been incorporated in the *Edinburgh Medical Journal*. I wonder whether the time has not come when, in the interests of both the Society and the Edinburgh School, we should reconsider their publication as was our custom—in conjunction with those of the Obstetrical Society, if that Society is agreeable—as a separate volume ?

The existing arrangement was, I understand, come to partly in view of mutual financial advantages. The *Journal* would benefit since it would acquire additional subscribers—members of one or other of the two Societies who had not previously subscribed to it—and in addition it might be more attractive and more representative of Edinburgh. Whether the circulation of the *Journal* was thereby materially increased I do not know. On the other hand, the Societies

might be expected to benefit since their communications would be brought to the notice of subscribers to the *Journal* who were not included on their Rolls of Membership, while another possible advantage to the Societies would be that their *Proceedings* would be published soon after delivery and not delayed until the end of the year.

Several publications which are now extinct were appearing in Edinburgh in the 'nineties—a period when the reputation of Edinburgh Medicine, using the term in its restricted sense, perhaps reached its peak. The *Edinburgh Medical Journal* then had its rival in the *Scottish Medical and Surgical Journal*, which was edited by William Russell and Norman Walker and supported by seceders who were dissatisfied with the publishers of the former at that time. Then there were the *Edinburgh Hospital Reports* which came out annually as a handsome volume; they were a credit to the School. Their pages include many valuable papers, some of them contributed by men who, had they not been urged by a sense of duty or *esprit de corps*, would probably have never put pen to paper. Why were our Hospital Reports allowed to lapse when those of some of the London Hospitals continue? The Laboratory of the Royal College of Physicians was also issuing each year a bulky volume of bound reprints, while both our *Transactions* and those of the Obstetrical Society were then appearing as independent entities. But to-day the *Edinburgh Medical Journal* and the *Honyman-Gillespie Lectures* are our only two representative medical publications.

Is it not possible nowadays to produce two successful publications in Edinburgh—the *Edinburgh Medical Journal* and the *Transactions* of this Society combined perhaps with those of the Obstetrical Society—each with its distinctive characteristics? A number of the communications to the Clinical Club are well worth publishing, and the proposed establishment of separate medical and surgical sections will, I think, act in itself as a stimulant. We cannot, of course, attempt to emulate in any way the *Transactions of the Royal Society of London* with that Society's great wealth of material, but we could, I believe, produce an annual volume of *Transactions* which, if well edited, might be most attractive and if effectively published and brought to notice might make a wide appeal. This is a question to which, I think, the Council should give careful consideration.



## SURGERY IN A JAPANESE PRISON CAMP ON SINGAPORE ISLAND \*

By J. A. P. CAMERON, F.R.C.S.Ed.

WHEN Singapore surrendered to the Japanese on 15th February 1942, orders were given that all patients in the General Hospital were to be removed within twenty-four hours to a hospital which was previously a Mental Hospital, and that no equipment or drugs were to be removed from the General Hospital. This meant considerable discomfort for the patients, caused many deaths, and called for a great physical effort by the European medical and nursing personnel who were already exhausted by overwork.

Europeans numbering about 3000 were rounded up, harangued in front of the municipal buildings and then marched from Singapore to a temporary camp consisting of a few houses at the seaside three miles away. Approximately 370 women and 63 children were crowded into houses nearby. Food and cooking facilities were sadly wanting, and the sanitation was shocking. After a week the whole camp was marched to Changi Civil Prison over five miles away, which was to be our abode for two and a half years. After that we were transferred to a wooden-hutted camp equally overcrowded but in many respects better, in that we led an open-air life with more freedom and facilities for outdoor work.

In the beginning the Japanese called a meeting of our medical staff, and gave permission for us to have a camp hospital with a staff of twenty-five persons of which only four were to be doctors, and such equipment as *they* considered was adequate for nursing and for minor surgical work. It fell to my lot to be responsible for the surgical work inside the camp. I would like to add how grateful I was for the co-operation and assistance I received from my surgical colleagues who gave their advice when difficulties arose and who carried out several of the major operations while I assisted and supervised the necessary preparations.

I was given permission to visit the Mental Hospital and obtain some of the essential requirements for surgical work—a table, instrument steriliser, dressing drums, a few instruments, surgical dressings, drugs and a small quantity of chloroform and ether.

Since the prison had been damaged by fire it took our engineers a few days to get the water and electric supplies in working order, and when this was achieved it was not long before we could use the

\* Read at a meeting of the Edinburgh Medico-Chirurgical Society on 3rd July 1946.

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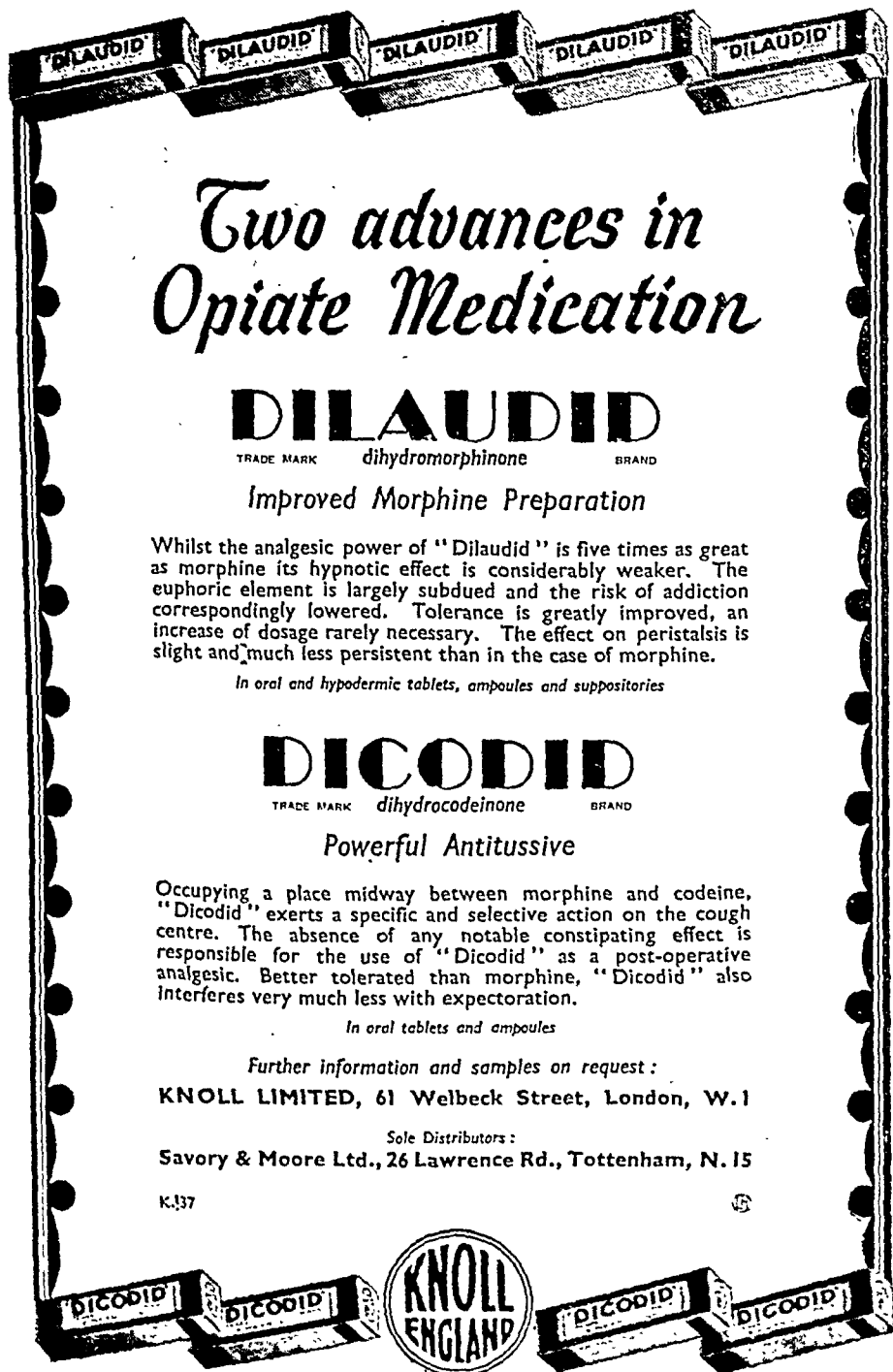
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prison steam disinfectors for sterilising dressings, etc. Electric inspection lamps and emersion heaters for sterilising water were made and fitted. I need hardly say that the chemists wasted no time in getting their paraphernalia together for distilling water and alcohol, and extracting suitable alkalis from wood ash, etc.

Our available surgical equipment and stocks were augmented by donations given by various people who had been able to conceal them in their bags on coming into camp. Each time the ambulance was allowed out we were able secretly, by the aid of our Asiatic friends in the outside hospitals, to add to the equipment bit by bit, until I soon had enough to perform any major emergency operation should the occasion arise.

The Japanese agreed to our using the Mental Hospital for major surgical cases, acute medical and infectious diseases, and allowed a surgeon, physician and ophthalmologist of our own to remain there. This arrangement was of inestimable value to the camp, both in regard to treatment and liaison with the outside world.

No communication was permitted with the women's section of the prison, and we were not allowed to employ our sisters or nurses. It was therefore necessary to select male orderlies whom we could train in surgical and ward work. The Salvation Army men were specially suited and became reliable workers. To begin with, I was allowed by the Japanese two theatre orderlies and one dresser for the ward. We had one surgical dressing-room or theatre and a small examination room, which, owing to the intense overcrowding in the prison, had to be used as a dormitory at night for some of the staff. Three dispensaries were installed in the prison and staffed mostly by those doctors who were in private practice before the war. An immense amount of medical and first-aid surgical work was done there, which relieved hospital out-patient work considerably.

As regards the ambulance, no objections were ever made by the Japanese to our using it night or day to convey emergency cases to the outside hospital, and we made the most of this privilege for a year or so. After that our own staff was brought into prison and conditions deteriorated there. By this time the prison hospital was able to take charge of most of the cases and do most of the major operations. In October 1943 all contact with the outside world was stopped.

In view of our very limited supply of drugs, anæsthetics, dressing materials, etc., and a period of internment which might last for one year, or even five, it was essential that all surgical work should be reduced to an absolute minimum. In addition to the necessity for dire economy, it was soon obvious that the health and resistance of the majority of internees made operative work an even more hazardous procedure.

In May 1944 the camp was transferred to Sime Road, an open wooden-hutted camp. To begin with we had no means of sterilising

apart from boiling, until a steam-pressure drum system was devised. An old kitchen was converted into a small operating theatre which had to be "blacked out" for use after dark.

The period of internment in Singapore gave ample scope for the study of nutritional deficiencies, occupational disorders, and reactions of individuals to prison life. Full advantage of the situation was taken by the close co-operation of the numerous doctors (120) in the camp who were able to keep a daily estimate of food values and the health conditions of over 4000 men, women and children who were subject to the dietetic fancies of the Japanese.

Before considering some of the surgical conditions, it must be pointed out that the lack of proper and adequate drugs and equipment made treatment reminiscent of ancient days. My records deal with the male portion of the camp (approximately 3000). The average age was 45—mostly men who, before the war began, filled posts in the local defence forces, or were too old for service; men who for the most part had lived for many years in the tropics as miners, planters, business men or Government servants.

The long walk carrying baggage, in the heat of the day, followed by ten days of acute starvation and discomfort, could not have initiated a period of incarceration in a more unfavourable way. Temporary dressing stations were swamped with cases of septic blisters, fungus infections of the skin, herniæ, fissures-in-ano and hæmorrhoids.

There was an early rapid loss of weight; 15 per cent. in the young, 20 per cent. in the middle-aged, and 30 per cent. in older men (percentage of usual weight). Blood pressures dropped to unusual levels. "Black-outs" became frequent. There developed a general loss of muscle tone with laxity of ligaments. Loss of height averaged 1 to 2 inches. I would like to discuss some of the more major surgical conditions first.

### INGUINAL HERNIA

Forty-two men had an inguinal hernia before being interned. Many had lost or left their trusses behind. One hundred and eighty-one developed an inguinal hernia while in camp. Of these, 27 had recurred from a previous operation. Eighty underwent operation during internment. Of these, 23 had recurred up to the end of 1944. This may seem a high rate of recurrence but it must be remembered that operation was performed only on those whose hernia was quite uncontrollable by any method, was painful, or showed signs of strangulation.

*The Types of Hernia.*—Many of the older herniæ were of the direct type bulging through the floor of the inguinal canal and prolapsing down into the scrotum, but the common type of hernia that developed while in camp was a bulge localised to the deep inguinal ring and somewhat external to it, which in some cases only progressed down the inguinal canal. I managed to get an imitation Brook's

truss made from wood, sorbo rubber and rubber straps made from the inner tubing of a motor tyre which gave support to this type of rupture. Patients were encouraged to continue their work and keep the abdominal muscles in tone as far as possible.

*Type of Operation.*—No one method of operative technique was used, as each case presented its own problem. One, however, aimed at stitching adequately the various fascial layers, reinforcing the fascia transversalis and strengthening the internal ring. Recurrences usually appeared at a new site. There was a type of patient who seemed to be doomed to have a recurrence whatever method was adopted. I used silkworm gut latterly and was satisfied with its results.

### APPENDICITIS

Incidence of appendicitis was interesting in view of the carbohydrate diet.

1942—12 acute, 5 chronic.

1943—3 acute, 3 subacute and 3 chronic.

1944—5 acute, 5 subacute and 3 chronic.

1945 (6 months)—17 acute, 3 subacute and 2 chronic.

One might say that appendicitis was rare during the first three years. In January 1945 a small epidemic began when 17 cases, presenting very definite acute clinical features were operated on and found to have an inflammatory condition of the appendix. It was significant that all these cases came from one of the Jewish huts where eggs and tinned meats were fairly plentiful. There was also a catarrhal infective factor present. Seventeen per cent. of the men had had an appendicectomy done prior to internment.

### PEPTIC ULCER

The true cases of chronic peptic ulcer fared badly as a result of the unsuitable camp diet, shortage of milk and alkalis, but those who previously had suffered from the nervous type of dyspepsia were improved and even cured. Speaking generally, peptic ulcer cases progressed slowly to the stage of pyloric obstruction when a short-circuiting operation was done. They were bad risk cases, but with the marked improvement that followed operation and in spite of the poor diet later, the risk was fully justified. One case died of persistent regurgitant vomiting in spite of many surgical attempts to rectify the condition.

Six cases of hæmatemesis occurred. Every effort was made to treat these cases by medical means. One died and five were operated on. On retrospection I feel that surgery might have been applied sooner with less risk to the patient in view of the inadequate medical treatment that was available. These cases were desperate surgical risks in circumstances where resuscitative measures were limited.

At operation large hard masses of fibrous tissue were found at the pylorus with a hair-like omentum stuck on to this gelatinous looking mass. The stomach and bowel everywhere were water-logged and unhealthy. The question of simple jejunostomy was considered, but the extra risk of doing a short-circuiting operation and so avoiding the depressing psychological factor of a feeding tube was thought to be justified. Partial gastrectomy, the operation of choice under suitable conditions, was not considered justifiable.

Perforations occurred from time to time. There were four cases in 1945 with peculiarly short histories: (1) Three weeks dyspepsia. (2) Two weeks dyspepsia. (3) No previous history of dyspepsia. (4) A few short attacks of dyspepsia.

These cases occurred within a few days of each other. It seemed as though a definite psychological factor was at play, since on each occasion that the camp received good news and fresh hopes were raised, one or more perforations took place.

From the women's camp there was a remarkable absence of emergency surgery. No gastric surgery was required and only one case of subacute appendicitis occurred in two and a half years.

I shall now discuss some of the more minor surgical conditions which, however, formed quite a major part of our work.

### PAINFUL SHOULDERS

I think we are all familiar with the condition of painful shoulder, called subacromial bursitis and periarthrititis by the Americans, though I prefer the terms adhesive capsulitis with or without degenerative "tendinitis." This was a very common condition and affected mostly men between 40 and 50 years who, in their younger days, had led an active life, but for the past year or two had had a sedentary occupation and were now called on to do manual labour necessitating carrying heavy buckets or tubs. Nearly every case had a history of sepsis or rheumatism prior to the onset of the condition. In many cases the ligaments of the shoulder joints were so lax that a condition verging on subluxation existed. My records include 21 cases ranging from acute capsulitis to the typical case of Codman's cheesy tumour which was relieved by operation. Several of the cases showed a cloudy chalky fluid on aspiration of the subacromial bursa.

Three distinct clinical types were noted:—

- (1) A shoulder strain followed immediately by acute pain over the front of the shoulder, extending down the arm, forearm and back of hand. Pain not unbearable but preventing lying on the shoulder at night.
- (2) A shoulder strain followed by a mild ache which passed off until the same night or the following night, when it became intensely acute and unbearable, necessitating sitting up or walking the floor all night.

- (3) A painful shoulder not related to any particular strain or injury, of gradual onset and getting worse after a few weeks and associated with neuritis extending down the arm, forearm and back of hand—more like a case of arthritis.

Clinically these cases had in common a tender spot over the front of the shoulder.

*Treatment.*—In the milder cases the arm was rested on a pillow at first and this was followed by radiant heat and exercises after the acute phase had subsided. In the more severe cases the subacromial bursa was aspirated and novocaine solution injected into it with great relief. Almost full range of movement was regained, although often some creaking was felt. None of the cases recurred.

In those resistant to treatment and where the shoulder pain had localised to the insertion of the deltoid a gentle manipulation was done under anæsthesia when that was available.

#### DUPUYTREN'S CONTRACTURE

An attempt was made to investigate the background upon which this condition developed. It became quite prevalent in those who were doing manual work. Apart from trauma no constant factor was found. Some showed evidence of associated toxic and metabolic factors such as gout, rheumatism, fibrositis, etc. I could not find any evidence of a hereditary factor. The origin of this condition still remains in doubt. It was not seen in females.

#### SNAPPING THUMB AND TRIGGER FINGER

This condition was associated with minor traumata to the hands and had a more definite toxic or infective focus as the underlying factor. Tenderness was first felt opposite the metacarpo-phalangeal joint of the affected digit which was then followed by an increasing difficulty in extending the flexed terminal digital joint.

Snapping thumb is commonly found as a congenital lesion, but it was not unusual in those using the grass sickle. I understand it was equally common with the women of this country who were handling shells in the munition factories. There is always a tender nodule felt opposite the metacarpo-phalangeal joint. Is it a xanthomatous change in the tendon sheath and tendon? The ring finger was involved in nearly every case—very similar in many respects to Dupuytren's contracture only affecting a different tissue. Conservative treatment was employed in every case though operative treatment is preferable. With conservative treatment the average length of time was three months.

*Ganglion of the Wrist and Tenosynovitis.*—This occurred amongst those employed as carpenters. One case of tenosynovitis was associated with oxaluria.



*Olecranon-Bursitis*.—This condition became prevalent during the two and a half years spent in prison cells with their cement floors and constant traumata to the elbow. Many methods of treatment were used. It was found that in those who received no treatment at all the bursa gradually disappeared after a few months. In two cases complaining of pain the bursa was excised and found to contain "melon seed bodies."

*Semi-membranosus Bursitis*.—Associated with chronic aching pain in the knee and down the calf following a strain of the posterior ligament of the knee-joint, and was met with mostly in those who were pushing carts and straining the back of their knees. In one case it had to be dissected out.

*Tennis Elbow*.—Strains of the common extensor origin were relatively frequent while lifting logs of wood or bags of rice, etc. There were two distinct groups of cases :—

- (1) Those more acute in onset and tending to clear up within a short period.
- (2) Those more chronic in onset and course, and very resistant to treatment.

In the first group the elbow could not be fully extended and responded to manipulation with or without a local anæsthetic. The second group had usually a history of some superadded focus of infection. The elbow could be almost completely extended. It was very resistant to treatment and is the type which in civil life usually requires fasciotomy and erosion of the common extensor origin.

*Epididymitis, warts, rodent ulcers and skin carcinomata* were all prevalent.

#### FIBROSITIS

Although fibrositis and sciatica were common complaints they were not nearly so prevalent as one would have expected, in view of the unpleasant conditions under which people existed. Of those cases that were seen, many had recurring attacks lasting weeks or months. While local anæsthesia was available many cases of acute strain and fibrositis were treated with good results, while the more persistent types of fibrositis involving the neck, rhomboid-scapular area and back responded to fasciotomy. Manipulations had to be reserved for cases especially resistant to other forms of treatment. Two cases giving the typical clinical features of prolapsed disc responded dramatically to a gentle manipulation followed by graduated exercises.

*Gout*.—Seventeen cases are on record. The majority had no recurrences after one year and all were cured by the end of 1944.

*Fractures of Ribs*.—It was not possible to come to any conclusions regarding the state of the bones following this long period of malnutrition owing to the absence of X-ray facilities. Fractured ribs, however, were of frequent occurrence and usually resulted from trivial injuries. Healing occurred after three to four weeks.

The shortage of drugs made the conservative treatment of anorectal conditions extremely difficult. For chronic *constipation* sulphur in palm-sugar was useful while it lasted. Red palm oil had a laxative effect on some and the opposite effect on others. A herbal infusion of "galengang" made by the chemists was found to stimulate peristalsis, but its effectiveness was not complete without the assistance of the abdominal muscles.

*Fissures-in-Ano.*—These occurred daily in acute and chronic forms—the former responding to injections of an anæsthetic in oil, while the latter usually required excision.

In the first few months of interment when the diet was deficient in all nutritional values and critically short of vitamin B, peripheral *nerve palsies* occurred. The peroneal nerve became very susceptible to trauma and pressure. Ten cases are recorded where paresis occurred and on an average lasted four or five months.

### CHRONIC ULCERS

Lastly, I would like to discuss the subject of chronic ulcers and septic lesions generally. Chronic ulcers formed one of the major problems during internment and presented many interesting points. During the early months smears were taken from ulcers for microscopic examination and only mixed non-specific organisms were found. It was a fairly true saying that any abrasion below the middle third of the leg would take weeks or even months to heal. Here the circulation was poor; it was an area most easily traumatised and susceptible to gravitational oedema. It was noted, however, that while operation wounds healed well by primary union, an ulcer in the same person might take weeks to heal. An ulcer usually began with a small abrasion or insect bite. Within twenty-four hours there would be redness round about, with oedema of the leg and foot and a painful lymphatic gland draining the area. At the actual site blister formation was common, and gradually the surrounding skin would change in colour from a deep red to purple and later to black necrosis. A systemic reaction might or might not be present.

It is significant to note that pellagra, which is known to result from a deficiency of the B<sub>2</sub> factor, occurred in epidemic form from May till October 1944, when ulcers and sepsis were also at their maximum incidence. The camp diet was never deficient in vitamin A, D or C. The shortage of vitamin B and B<sub>2</sub> complex was always dangerously low. One of the factors in the etiology of ulcers which must be taken into account more than before is that of hypoproteinæmia and perhaps shortage of fat in the diet. In fact, it cannot be said that ulcers result from the shortage of any one factor in the diet but rather the result of an unbalanced diet deficient in good quality proteins and probably the B factors.

*Treatment.*—Plain fomentations repeated as often as possible or

kept warm with a hot bottle or brick with the leg elevated reduced the œdema and inflammation in the acute stages. As soon as the ulcer was clean a vaseline or "tulle gras" dressing was applied and the foot and leg were supported by a rubber latex bandage. This was kept on for two or three weeks and renewed if necessary. This technique allowed the patient to be ambulatory, was comparatively comfortable, saved dressing material, prevented interference and protected it from contamination.

From approximately the middle of 1944 a change was seen in some of the ulcers. The small ulcer, with its dark purple areola developed rapidly into a large gangrenous black slough which was dry or shiny, tough and adherent, and had to be excised. In some cases this was followed by peripheral neuritis, paralysis and death.

On microscopic examination of the smear from some of the ulcers diphtheria bacilli were seen.

My view is that all the ulcers were primarily of nutritional origin and produced chronic sepsis. A state of hypoproteinæmia existed. Further ill-health occurred and interfered with the utilisation and metabolism of the vitamin B factors in the bowel. When resistance to infection was at its lowest ebb, in some cases diphtheroid organisms began to flourish and added an additional toxic factor. This would account for the great variation in the severity of the neurological symptoms. The response to vitamin B therapy was variable and even misleading. There was always a slight general improvement noticed, but it cannot be stated that any visible improvement occurred in the ulcers or in the neurological symptoms in the early period of treatment, even with large doses of vitamin B therapy. Patients usually became slowly worse under treatment for several weeks and they improved gradually later. It was not possible to give any anti-diphtheritic serum in treatment, but one could anticipate mixed results in view of the somewhat uncertain etiology. It is possible that the incidence of ulcer contamination and peripheral neuritis might have been much higher if excision of the slough followed by the closed dressing technique had not been adopted.

## DISCUSSION

*Mr Millar* assumed that the large numbers of herniæ were due to marked loss of tone in the muscles due to malnutrition. He had come across a patient who claimed to have had bilateral inguinal hernia which had quite disappeared with the improvement in conditions resulting from his release from the camp. Mr Millar had been unable to find any sign of hernia on examination.

*Mr W. V. Anderson* asked if the painful shoulders were mainly bilateral and also if they were occupational in nature. During the war he had come across many cases of tenosynovitis in munition workers.

He was interested to know if the latex Mr Cameron had used had produced skin irritation through lack of ventilation, as was common here with elastoplast.

# SEVERE BURN (Area 162 sq. inches)

## A treatment using tulle gras, pressure dressings and plaster fixation



Fig. 1

**CASE HISTORY**—The patient, a young man, was admitted to hospital, having been burnt by an electric blanket. The raw area measured 162 square inches. Excision of the burnt area was performed on the same day. Tulle gras (Jelonet) was applied. Fixation by Gypsona plaster of Paris bandages applied over the whole area, abdomen and thigh. The patient was given a blood transfusion.

Seven days later, the affected part was covered with thin razor grafts from both thighs and a pressure dressing of Elastocrepe applied. Fixation was again secured with Gypsona plaster of Paris.

The patient was discharged to duty 7 weeks later.

The details and illustrations above are of an actual case. T. J. SMITH & NEPHEW Ltd., Hull, manufacturers of Elastoplast, Elastocrepe and Jelonet, are privileged to publish this instance, typical of many, in which their products have been used with success in the belief that such authentic records will be of general interest.



Fig. 2



Fig. 3

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*Mr Jeffrey* discussed the question of chronic ulcers. In the Middle East and Burma it was found that the recent ulcers were due to staphylococci and the more chronic ones harboured streptococci.

With reference to epididymitis he had seen many cases in serving soldiers. The condition was not usually gonococcal, but non-specific and secondary to prostatitis.

*Mr Jeffrey* commented upon the prevalence of fractured ribs and assumed that this was because the bones were so decalcified that they fractured easily, and he asked about the rate of healing in fractures of long bones.

*Mr R. L. Stewart* and *Dr A. B. Smith* also took part in the discussion.

*Mr Cameron*, replying, stated that circumcision had been a very common operation in their camp. Patients got a small ulcer crack at the mucocutaneous junction, apparently due to malnutrition.

At first, shoulder conditions were difficult to treat owing to the lack of physiotherapy. In time, however, they had succeeded in organising this in a small hut under the charge of two or three medical officers. With the help of the electrical engineers they managed to improvise different forms of treatment. The hot plate, for instance, was upturned and used in applying heat.

Ear, nose and throat cases formed a large part of their early work. Otitis externa became prevalent along with ulcers and general sepsis. They had difficulty in treating them, trying various methods. Usually they went on the principle of trying to keep them clean and dry. They had a good deal of cellulitis following otitis externa and treated it with sulphanilamide which gave good results.

About chronic ulcers, *Mr Cameron* could not say whether staphylococci were more prevalent in the early cases and streptococci in the later ones. Smears taken showed mixed infections, Gram-negative bacilli being the most prominent organisms. When they got the diphtheritic lesion the smear showed large numbers of the typical organisms. This was interesting because they got toxic peripheral neuritis in some who had never had an ulcer before. He recalled one case who had chronic diarrhoea and who eventually developed toxic peripheral neuritis. Another man had a perforation of a duodenal ulcer and the wound had gone a little septic. Later he developed a severe peripheral neuritis of which he died. It was difficult to be quite certain whether such cases were due to the actual diphtheritic toxin or not.

With regard to amputations, they had carried out one on a coolie. A weight had fallen on his toe and he later developed gangrene, but the Japanese refused to give him any treatment. He eventually came into their hospital and a Sime's amputation was done. It had not been possible to follow up his case, but he was last seen on crutches—the wound having healed by first intention.

Epididymitis was very common and usually followed a slight trauma. There was never anything in the urine to suggest a *B. coli* infection. It usually lasted for about three weeks and required rest, which seemed to be all that was necessary. Sulphapyridine was tried but did not seem to help.

With regard to decalcification of bones, *Mr Cameron* was unable to make any definite statement owing to lack of X-rays for confirmation. Fractures such as Colles, Pott's, etc., were successfully treated in plaster while plaster was available. He recalled two cases of fracture of the neck of the femur,

one of which was treated conservatively in splints and in time had very solid union. The other, a man of 60, had a sub-capsular fracture. Nursing was difficult and treatment by splinting was a problem so they decided to operate. Open operation was carried out and a Smith-Petersen nail was inserted, the appropriate instruments for this being made by a camp engineer. The patient made a comfortable and uneventful recovery.

Mr Cameron's impression was that those with herniæ would improve with better conditions and he was interested to have this confirmed by Mr Millar.

Mr Cameron could not say whether shoulder lesions were more marked on the right or the left sides. He too had noted peripheral neuritis with burning feet, and he attributed this to lack of vitamin B<sub>2</sub>. It was a most distressing condition, but used to clear up in ten days or so under treatment with Marmite. Drop foot was usually treated with elastic suspension applied in such a way as to enable the patient to get about.

With regard to latex, Mr Cameron had never found any skin irritation such as is usually associated with elastoplast. After three weeks the skin was quite clean except around the actual ulcerated area where there was usually some moisture, but after three days or so of exposure to the air this healed up quite satisfactorily. A latex bandage gave excellent skin traction for fractures and was a good supporting bandage for varicose veins.

# VIRAL INFECTIONS OF THE CHICK EMBRYO RESPIRATORY TRACT

## I. CONTROL OBSERVATIONS

By J. H. FODDEN, M.D.(Leeds), Department of Pathology, The University of Liverpool; and A. J. RHODES, M.D.(Edin.), F.R.C.P.E., Department of Bacteriology, London School of Hygiene and Tropical Medicine.

## INTRODUCTION

FOLLOWING early work of Gallavan and Goodpasture (1937) on bacterial infection, it has been found that various viruses can also proliferate in the respiratory tract of the developing chick embryo, when inoculated directly in the amniotic cavity. Most work has been carried out with influenza virus, which produces characteristic changes (Burnet, 1940*a* and *b*), but the viruses of mumps, herpes, psittacosis and infectious laryngotracheitis also proliferate.

Advantage is taken of this susceptibility of the chick embryo respiratory tract to influenza virus in one method of laboratory diagnosis. Throat washings are injected in the amniotic cavity of thirteen- to fourteen-day embryos, which are then incubated at 35-36° C. for three days. The presence of infection is judged by the occurrence of agglutination when a few drops of amniotic fluid and a 2 per cent. suspension of fowl red cells are mixed in a watch glass. A valuable confirmatory finding is the presence of characteristic changes in the lungs (Burnet, 1940*a* and *b*; Fodden and Rhodes, to be published; for a review of the methods of laboratory diagnosis in influenza, see Rhodes, 1947).

The normal histology of the chick embryo lung is, of course, well known to embryologists (Gadow, 1893; Juillet, 1911-12; Kerr, 1919; Lillie, 1919; Bremer, 1939). This information is, however, less familiar to medical laboratory workers who may undertake the laboratory diagnosis of influenza, or otherwise wish to examine histologically the lungs of virus-infected embryos. Accordingly, for the guidance of such medical workers, we wish to record our own observations regarding the appearances to be expected in the normal chick embryo respiratory tract, when examined by routine morbid histological technique. It is to be understood that we make no claim for the novelty of these observations, and our paper is not intended as a contribution to embryological literature. In a later communication we shall describe the changes in viral infections.

## METHODS

*Chick Embryos.*—All eggs were supplied by Mr Y. Watanabé, Cobham, Surrey, and a very high fertility rate was obtained. The



eggs were from Light Sussex hens crossed with Rhode Island Red males or Rhode Island Red hens crossed with Light Sussex males. Eggs were incubated, the day after arrival, in a Hearson gas-operated egg incubator, set at 38-39° C.; they were turned daily, and the water tray in the incubator was kept filled to the prescribed level.

When eggs had reached the desired day of development they were candled, and opened if fertile and living. The embryos were then decanted into a petri dish, quickly freed from the yolk-stalk, and placed in 5 per cent. formol-saline. The embryos usually "gulped" for some few seconds, and some fixative may have reached the proximal respiratory tract directly. Embryos were kept intact in fixative for four days prior to examination, to allow of complete penetration.

We have examined over fifty embryos at all stages of development, from the fourth to the twenty-second day, concentrating on those at about twelve to seventeen days, the crucial period in amniotic inoculation.

*Control Procedures.*—Preparatory to studying the effect of influenza virus on the chick embryo, it was decided to carry out some control inoculations with non-infective material. A number of thirteen- to fourteen-day and some seventeen-day embryos were accordingly inoculated in the amniotic cavity with 0.15 or 0.2 c.c. of sterile broth or saline, following a method based on that of Burnet (1940*a* and *b*), which has been separately reported (Rhodes, 1946). The eggs were then incubated in an ordinary bacteriological incubator, without moisture, at 36° C. for two to six days.

Several nine-day embryos were also inoculated in the allantoic cavity with 0.2 c.c. of broth or saline, and incubated at 36° C. for two or more days (Burnet, 1941).

In order to control the effect of changing the temperature from 38-39° C. to 36° C. a few embryos were merely changed to the lower temperature at the appropriate period of development. Some were changed after nine days incubation at 38-39° C., and others after thirteen days incubation. The period for which the eggs were maintained at the lower temperature varied from one to four days.

*Histological Examination.*—A transverse section of the thorax was made across its widest part, and the material blocked in paraffin in the usual way. Sections were cut so that some included the hilar regions, and others the regions of the lungs above and below this level. A transverse section of the neck was also made, for examination of the trachea. Sections were stained by Heidenhain's azan method for collagen, and connective tissue; by Heidenhain's hæmatoxylin method; by Dublin's (1946) silver method for basement membrane and reticulin; when necessary, additional sections were stained by Weigert's resorcin fuchsin with van Gieson, and by Mayer's mucicarmine method.

## THE TRACHEA

The trachea is lined by a stratified epithelial layer of tall columnar cells. It is difficult to recognise in every section the ciliated surface membrane, which is more easily demonstrated between the fifteenth to twentieth days of development. Later an apparent stratification still exists, though the epithelium is less crowded with cells, which are of a lower columnar type. They have a dark-staining, spherical nucleus, which is usually basally, though sometimes centrally placed. Many of the cells have a clear cytoplasm swollen by a mucus vacuole. Some of the vacuoles appear to have ruptured on to the surface, and discharged their contents into the lumen. The epithelium rests upon a thick, rather wavy basement membrane, below which is a narrow compressed reticular submucosa. Numerous capillary blood vessels are present within this zone. The tracheal lumen is clear of all cellular and granular debris.

## THE LUNGS

*The Mesobronchi.*—Up to about the sixth day of development the most prominent epithelial structure in the pulmonary tract is the mesobronchus (see Figs. 6 and 8), which extends from the hilum throughout the pulmonary mesenchyme. It has a thick wall, and its lumen is wide and circular. The lining is composed of tall, stratified columnar epithelial cells of two distinct types. Very tall conical-shaped cells with densely-stained cytoplasm, and a dark basally-placed nucleus, are found infrequently between larger cells with a clear, bulky, faintly granular cytoplasm and a large pale granular nucleus. The cytoplasm of some of these latter cells is swollen into a goblet shape by a clear mucus vacuole. A thin continuous surface membrane crowded with cilia is usually evident (Fig. 6).

The epithelial lining of the mesobronchus rests upon a complete thick basement membrane best demonstrated by silver staining. Below the membrane is a narrow reticular submucosa, derived from mesenchyme, composed of thin darkly-staining spindle-shaped cells, arranged in an orderly concentric fashion. Before this zone blends indefinitely with the paler mesenchyme, it is traversed by an irregular layer made up of bundles of dark-staining, laminated, long cylindrical cells. These cell-aggregations are those of developing smooth muscle, and this layer becomes the muscular wall of the mesobronchus. A similar layer is prominent in other structures derived from the mesobronchus, and will be referred to as the developing muscular wall.

*The Entobronchi.*—As development proceeds, the regular outline of the mesobronchus is very quickly altered by outgrowths of many variable-sized entobronchi, best seen about the seventh day. Their appearance alters quickly by a continuous and rapid process of evagination of the whole of the wall, with the formation in the

mesenchyme of many smaller, regular tubules, the tertiary bronchi or parabronchi (Fig. 5). The microscopical structure of the entobronchus is the same as that of the mesobronchus, except for variation in the thickness of the condensed mesenchyme forming its submucosa. This layer is narrower, and the mesenchymal cells are less compact. The developing muscular layer is still present, though much thinner and more regular.

*The Parabronchi.*—The parabronchi are seen to increase enormously in number progressively from the ninth to the thirteenth day. There is also a considerable concomitant growth and expansion of the mesenchyme, to accommodate the larger number of tubules. On cross-section, the parabronchi appear as circular epithelial tubes, on longitudinal section as regular cylinders (Fig. 1). Their epithelial wall is formed of closely packed fairly tall columnar cells. These cells are so closely crowded together that cytological details are

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FIG. 1.—Photomicrograph of parabronchi on the 12th day. Hexagonal areas of mesenchyme are becoming outlined by developing blood vessels. Cleft formation within the epithelial lining, and the thin muscular coat are shown.  $\times 100$ . Heidenhain's Hæmatoxylin.

FIG. 2.—Photomicrograph of parabronchi on the 12th day, to show the complete epithelial basement membrane and the hexagonal arrangement of developing blood vessels.  $\times 150$ . Dublin's Silver Method.

FIG. 3.—Photomicrograph of parabronchi on the 14th day to show the more advanced state of cleft formation in the epithelium, with early evagination through the embryonic muscle layer.  $\times 150$ . Heidenhain's Hæmatoxylin.

FIG. 4.—Parabronchi on the 15th day of development showing well-formed tubular epithelial evagination through the thin muscle layer. Note the change in the epithelium from a columnar to a lower cuboidal type.  $\times 150$ . Heidenhain's Hæmatoxylin.

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extremely difficult to define; they are devoid of cilia. The cytoplasm is faintly acidophilic and slightly granular, though some cells appear to be full of dark chromatin granules. The nuclei are small, spherical, darkly-staining, and are more commonly basal than central. Many nuclei show mitotic division. Silver staining shows a thin complete basement membrane (Fig. 2). Closely applied to this membrane, though separated from it by a few thin mesenchymal cells which form the submucosa, is the narrow layer of embryonic muscle. It is identical, apart from its width, with the layer surrounding the meso- and entobronchi. This layer is sometimes only one or two cells wide, and often complete gaps exist. Loose, cellular mesenchyme everywhere surrounds the parabronchi.

*"Sacculation" of the Parabronchi.*—About the thirteenth to fifteenth day, the epithelial lining of the parabronchi becomes divided by wide clefts at regular intervals (Fig. 3). The cells between these clefts are heaped-up, and show irregularity of size and arrangement with a denser nuclear structure. The clefts extend down to the basement membrane, which is unaltered by this epithelial activity.



FIG. 2.

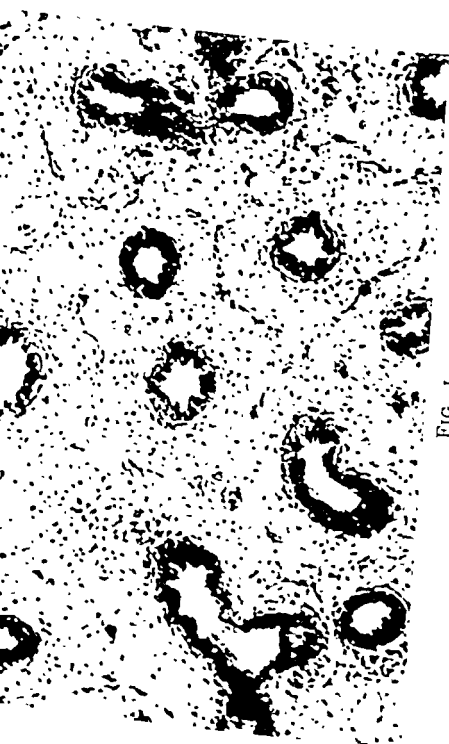


FIG. 1.

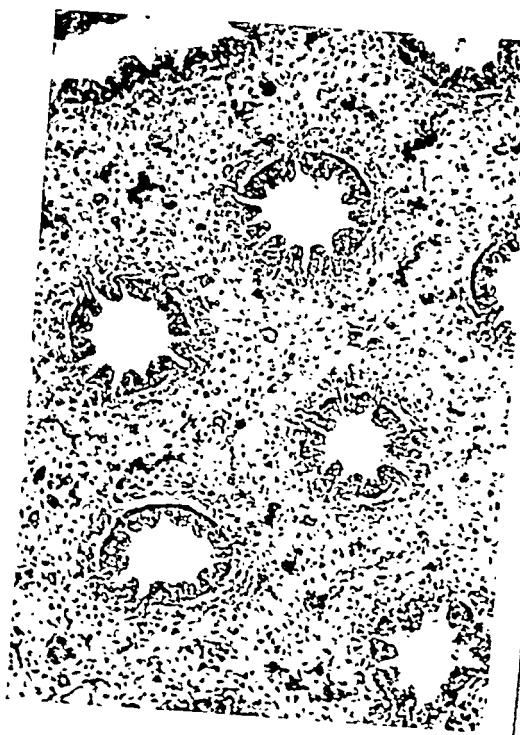




FIG. 6.



FIG. 5.



However, on the fifteenth and sixteenth days the basement membrane bulges outwards in front of the expanding epithelium-lined clefts, which have now become definite evaginations from the wall of the parabronchus. The evaginations grow through, and completely disrupt the thin muscular layer of the parabronchus (Fig. 4). They extend into new areas of mesenchyme, leaving behind the submucosa and muscular layer of the wall of the parabronchus. Silver staining shows their epithelial wall to have a thick basement membrane derived from and continuous with that of the parabronchus (Fig. 7). A change in the epithelium also takes place at this stage. The stratified columnar-cell epithelium of the parabronchi becomes replaced abruptly at the site of each evagination by a single layer of cuboidal cells. As the tubular "buds" near completion, the epithelium of the "parent" parabronchus becomes similarly cuboidal.

The muscular wall of the parabronchus is now represented by

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FIG. 5.—Parabronchi on the 16th day of development. The mesenchyme between the epithelial units is becoming more condensed, and a few air-capillaries have already formed. An entobronchus is seen in the lower left of the illustration.  $\times 150$ . Heidenhain's Hæmatoxylin.

FIG. 6.—High-power photomicrograph of the epithelial lining of the mesobronchus on the 20th day. The ciliated surface membrane can be seen. Note the thick dark-staining developing muscular wall.  $\times 300$ . Heidenhain's Hæmatoxylin.

FIG. 7.—Parabronchi on the 15th day of development. This shows the evagination of the basement membrane of the parabronchus, along with the epithelium during the formation of air-capillaries (*cf.* Fig. 4).  $\times 300$ . Dublin's Silver Method.

FIG. 8.—This shows the mesobronchus surrounded by epithelial air capillary units on the 21st day of development. Note that the mesenchyme has now assumed the structure of a supporting stroma between such units.  $\times 150$ . Heidenhain's Hæmatoxylin.

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small segments of smooth muscle which lie in the narrow bands of mesenchyme between the many air-capillary tubules. These segments form a sphincter around the junction of all the air-capillary tubules with the parabronchial lumen. By the twentieth day the whole process of evagination from the parabronchi has formed a unit of numerous air capillaries known as the labyrinth.

*The Mesenchyme.*—In the early days the lungs consist largely of undifferentiated mesenchyme, which rapidly becomes more spacious and cellular. It is composed of stellate cells with a clear cytoplasm and a small centrally placed, dark-staining nucleus. These cells are arranged in a loose reticular network, and are linked to one another by thin strands of protoplasm that stain faintly with silver, and the aniline blue of the azan.

About the seventh to the ninth day of development the mesenchyme is divided into regular hexagonal areas by developing blood capillaries, composed of short, spindle-shaped, darkly-staining cells. Lumina appear in these capillaries about the thirteenth day of development. During the formation of the labyrinth, numerous short cellular branches

from these primary blood vessels dip between each cellular bud and tubule, and the whole labyrinth becomes surrounded by minute vascular capillaries. Each hexagonal area of mesenchyme becomes rapidly compressed towards the periphery by the growing evaginations, its reticular structure disappears, and its component cells become dark-staining oval-shaped dots. Tubular air-capillaries, each lined by flattened cuboidal cells, with a dark oval-shaped nucleus occupying most of the cell protoplasm, form an inter-connecting unit (the labyrinth) which almost completely replaces the original mesenchyme of the hexagon. The unit retains the hexagonal shape determined by the primary vascular network. The mesenchyme is now represented by sparsely cellular supporting stroma only.

*The Blood and Lymph Vessels.*—It is within the narrow stroma that the larger pulmonary blood vessels travel, and give off the fine capillary branches to the labyrinth. These small arteries and veins are developed in part from the dark-staining cells which compose the original vascular hexagon. These cells probably form only the endothelial lining of these vessels, and a blood-filled lumen is apparent amongst them before other components of a vessel wall are recognizable. The muscular and adventitial layers which are seen about the seventeenth to the twentieth day of development are formed during the later stages of mesenchymal compression and differentiation. The azan stain shows a condensation of short spindle-shaped cells from the mesenchyme arranged in a concentric manner around the endothelial cells. Lymphatics become apparent in the mesenchyme about the twentieth day of development as small irregular spaces accompanying the larger blood vessels. Their wall is formed of only one layer of thin mesenchymal cells, and their lumina are free from all cellular or particulate matter.

#### EFFECT OF CONTROL PROCEDURES

The inoculation of broth or saline into the amniotic cavity of thirteen- or seventeen-day embryos brought about no histological variation in any of the anatomical structures detailed above.

Inoculation of sterile fluids into the allantoic cavity in no way altered the progress of development or the microscopical appearance of the normal lung.

Removal of embryos from 38-39° C. to 36° C. produced no developmental or histological changes from the normal.

#### SUMMARY

An account has been given of the histological appearances to be expected in the normal chick embryo respiratory tract, with particular reference to the period of development of importance in amniotic inoculation of viruses.



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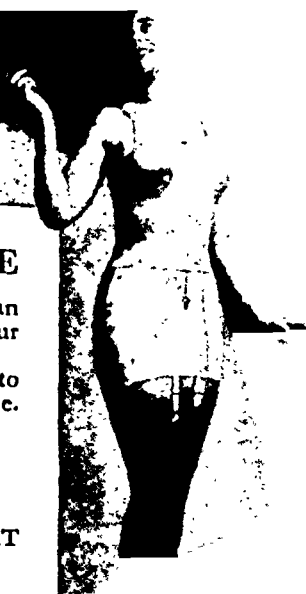
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## TREATMENT OF THE DEAF

### HEARING AIDS AND THEIR MODERN CONCEPTION \*

By G. EWART MARTIN, F.R.C.S.Ed.

*Types of Deafness.*—In discussing the problem of deafness we must distinguish at the outset between the so-called "hard of hearing" who tend to conceal their deafness, in fact who claim they are not deaf, and the "actual deaf" who have no sense of hearing. These latter may be congenitally deaf or have lost their hearing before they acquired speech and in the old terminology were called "deaf and dumb." Also in this group of the "actual deaf" are those who have lost their hearing in later life through accident or disease but who have retained their power of speech. The term "deaf and dumb" is of course an entirely obsolete one because by modern educative measures deaf-mutes can be taught to speak. Those who have lost their hearing entirely by accident or disease can be trained also by educational methods to maintain their proper place in society.

In this discussion, however, we are concerned with the "hard of hearing." It is not possible to group these cases. They can be slightly hard of hearing, moderately deaf, markedly deaf, extremely deaf, in fact going on to almost total deafness when presumably they would come under the second group.

The terms are admittedly confusing and they are made worse by the fact that the patient conceals the deafness and never wants to be told he is deaf.

*History of Deafness.*—Chronologically the history of deafness offers many interesting features. They are mostly concerned with the totally deaf. In the present day the deaf child must be considered not only as a clinical entity but as a vital factor in the economics of any country, while in the days of Aristotle the deaf and dumb child was considered of less use than an animal and was destroyed. Much has been written and much tried by the old philosophers to educate these people, but little mention was ever made of the hard of hearing—possibly they managed to conceal their deafness. The first hearing device does not appear in literature until about the seventeenth century when Ellipsis Otica was described for amplifying sounds.

The problem is more acute to-day and the hard of hearing are admitting they are deaf and are seeking advice.

In the spring of 1939 I read a paper before the Society with the title "In Search of Hearing."

\* Read at a meeting of the Edinburgh Medico-Chirurgical Society on 5th June 1946.

The modern world relies more and more on the spoken voice rather than the printed word. This was emphasised over and over again during the war. The moral of the country would not have remained so high if our leaders had communicated by pamphlets or the press instead of coming to the microphone and talking to the nation.

Therefore during the last six years the public have been dependent on the wireless. Unfortunately very few new wireless sets were available. Repairs have been impossible and many people have had to listen to distorted reproduction, and this was quite unintelligible to people over the sixties who were showing early signs of senile nerve deafness. Consequently they began to seek advice.

As a result of the war with its nervous tension, its rationing and its blackout, senile nerve deafness has begun to show earlier than in the past.

Recent research has shown that unfortunately deafness as a whole is on the upgrade. (This includes middle-ear deafness as well as perceptive deafness.)

*Otitis Media.*—Recent investigation into the case records of ear disease in the Department of the Royal Infirmary under my charge show that since the use of sulphonamides, cases of otitis media have been reduced to almost half. At its face value this was extremely encouraging, but the mastoid and intracranial complications had actually increased showing that the percentage of complications has been more than doubled. On further investigation into individual cases we were appalled by the amount of deafness. The acute ear may lose its symptoms with the use of sulphonamide, but in a great many cases the results of the acute infection remain, fluid forming behind the drum does not absorb, adhesions form and the patient remains deaf—a deafness which, in the majority of cases, cannot be improved.

Similar investigations in other hospitals have corroborated these findings. There has, therefore, been a larger percentage of deafness in otitis media in recent years.

*Medical Research Council Committees.*—The Medical Research Council have appointed a committee to enquire into the medical and surgical treatment of the deaf. This committee has not finished its findings so that little can be said about the methods to be adopted in an effort to prevent deafness of this type. Many consider that otitis media should be a notifiable disease.

The Medical Research Council also appointed a second committee—electro-acoustics. This committee has finished its deliberations on the design, performance and application of electro-acoustic equipment used in the investigation and alleviation of deafness and has initiated such fundamental investigations as it considered necessary in such connection.

The report of the committee is in the hands of the publishers and we cannot so far discuss it but we know that an efficient hearing aid

has been devised adopting a circuit much more simple than previously used by the makers of reputable hearing aids.

This instrument is comparatively cheap to manufacture but no measures have been taken yet for its production and supply.

It has been recommended that arrangements might be made through the Ministry of Supply for the mass production of this hearing aid by the present hearing aid manufacturers and that the aids should be dispensed through special clinics attached to the otological clinics of the larger hospitals.

Unfortunately news of this instrument has been published, even in Parliament, before any action has been taken as regards its production or prescription.

However efficient this hearing aid may be it is by no means the complete answer to the problem of deafness. No hearing aid can be universal. Its type should depend on the character of the patient's deafness.

In the past the public have been scandalously misled by advertisements for hearing aids. Even stamp books supplied by the Post Office had glowing advertisements of "deaf ears hear again." Naturally deaf people answered these advertisements and were handed hearing aids across the counter—hearing aids of use in a very small percentage of early middle-ear deafness but detrimental to a perceptive deafness.

We otologists were definitely to blame for not preventing the exploitation of the deaf by firms manufacturing these instruments. The prescription of hearing aids was not considered the duty of the otologists who were concerned with disease of the ear, not its diminishing function. Only a few otologists were interested in acoustics.

The subject of hearing aids was little ventilated until twelve years ago and we are indebted to Cleminson, Terence Cawthorne and Phyllis Kerridge for much of the early work on hearing aids. In 1937, under the auspices of the late Dr Kerridge, a clinic was instituted in University College Hospital, London, for giving advice on hearing problems. It provided a centre for investigation and for demonstrations to medical students, doctors and teachers of the deaf. It did much to reduce the price of the advertised mass produced hearing aids and it brought to the minds of the otologists the fact that many firms interested in radio and acoustics were experimenting on the making of valve aids. The only form of reimbursement these firms had for their experimental work was an added cost to the price of the instrument so evolved.

Attempts were made to start a hearing aid clinic in Edinburgh but these fell through owing to the fact that the makers of hearing aids could not service them in Edinburgh nor could they have representatives on the spot. One or two well-known hearing aid manufacturers opened agencies in Edinburgh.

We felt that a hearing aid clinic outside an ear, nose and throat department was not actually scientific. It might lead to hearing

aids being prescribed for patients whose ear condition really precluded use of an aid, such as a perceptive deafness with a very low upper tone limit or a perceptive deafness accompanying a disseminated sclerosis.

### TYPES OF HEARING AIDS

As I mentioned in my last communication there are two main types of hearing aids, (1) non-electrical (2) electrical.

*Non-electrical hearing aids* (apart from minor alterations) have been used for the last one hundred years. These hearing aids are unpopular because of their conspicuousness, but still they are the only hearing aids which should be used in certain types of deafness. The principal types include the various forms of resonators, ear trumpets and speaking tubes. They are merely conductors of sound and not amplifiers, whereby the natural voice is well reproduced without distortion. The banjo ear trumpet is possibly the best of this type of instrument. It can be produced cheaply but, unfortunately, the public have never forgotten Punch's well-known suffragette cartoon "aye toot and y're oot" so this is an instrument which no one likes to produce in public. In an effort to make these aids less conspicuous, auricles have been constructed with small flattened ear trumpets held by a band to the head with the sound conductors pointing forwards. These are almost too directional and not nearly so proficient as the larger type of ear trumpet.

The oldest form of non-electrical hearing aid is the one we all carry about with us and which can be noticed in use by nearly half the audience at any meeting—that is the hand placed behind the ear, cupped to direct the sound towards the ear.

The physiological change of old age in the cochlea gives a lowering of the upper tone limit making it difficult to pick up the finer sounds. There is also a central change which results in a difficulty in separating sounds. A child can comfortably separate out three groups of sounds, an adult, as we all know, can converse with one person and yet have an inkling into the general conversation of the room. However there comes a time when sounds cannot be separated and though a tête-à-tête conversation can be heard in a quiet room nothing can be heard in a noise. The individual cannot keep up a conversation if two people are talking at the same time. Where the sounds cannot be separated no form of amplification will allow the general conversation to be heard as the electrical aid amplifies the surrounding noise as well as speech. All that is required is something to direct the sound towards the ear and cut out other noise. This can be done with a directional resonator or in the more advanced cases a speaking tube; and there is no reason why such a deaf person should not carry on a conversation with his neighbour using a speaking tube during the buzz of general conversation, whereas without the speaking tube he would only hear the buzz and not the conversation. Unfortunately

this type of patient tries to conceal his deafness and in a noisy room edges close up to the person he is conversing with who has to raise his voice to an unnatural pitch—an embarrassing situation if there is a sudden pause in the general conversation.

*Electrical Hearing Aids.*—1. The micro-telephone; this is simply a microphone constructed of rough carbon granules energised by a battery and with a small ear-piece. Actually the microphone can be doubled or trebled to get larger amplification and instead of the ear-piece worn over or fitted into the ear a bone conductor held on the mastoid process can be used.

This type of micro-telephone gives a 16 decibel amplification only and is usually noisy, at least the machine manufactured instruments must necessarily be. It is essentially wearable. In the past it was the only known electrical instrument, and unfortunately laid itself open to mass production. It is of use in the very mild cases of middle-ear deafness or in an early otosclerosis—patients who usually hear better in a noise. It proved a definite aid until the otosclerotic developed a nerve involvement as well when the instrument was a danger. It is definitely detrimental to the perceptive deafness.

This type of instrument could be made at very small cost. I had a hand-made instrument constructed for use in the consulting-room at the cost of 17s. 6d. This was a copy of an instrument which sold for seventeen guineas—not a bad profit. However, considering that the firms were spending £600 a week on advertisements there had to be a profit somewhere. The difficulty arose in that these instruments were handed across the counter—some firms pretended to do a hearing test as a bait. The deaf person wishing to get in touch with the outside world fell, and came later to the otologist with the tale of woe that he just could not hear with or without the instrument. The otologist could give little help. At present the hand-made micro-telephone with special microphone and bone conductor gives very good results in picked cases of early middle-ear deafness where a wearable aid is essential.

2. The valve amplifier. These aids have developed along with the development of radio. Originally they were clumsy, unwearable and scarcely portable because of the necessity of the heavy high tension battery and the large low tension battery or accumulator.

Before the war very small radio valves were employed and batteries were slightly less in size. One or two firms had actually produced a wearable valve aid but the batteries were still rather clumsy and heavy to carry. However, the patient could wear the aid with a certain amount of inconvenience.

The war has changed all this. The army had to use radio as a means of communication, small radio sets had to be fitted into tanks, they had to be carried and they had to be flown. The minutest instruments were sent up in balloons for experimental work at high altitudes. The instruments had to be made smaller and yet efficient

which required a lot of experimental work and no individual firm could have financed this work. However, the makers of these instruments are reaping now the benefit of the experiments. The radio valves are almost the size of a pea, the transformers not bigger than the thumb nail, the microphone almost the size of a shirt button, and, most important, the batteries can be constructed no bigger than a matchbox and yet give a 50 volt potential for a longer period than the old cumbersome high tension battery. The low tension battery need be only 1 to  $1\frac{1}{2}$  volts to heat the small pea valve. All this means that the valve aid can be made wearable. These wearable aids are to a certain extent flimsy and are of little use to the manual worker except as an occasional aid.

Once again it must be emphasised that no hearing aid is universal.

The price of these aids is still a consideration. It has been estimated that the circuit devised by the Medical Research Council could be marketed for about £8, possibly less to hospital patients.

The reason for the extra cost of instruments made by reliable manufacturers is that they have to allow patients a trial of the machine before purchase. With an electrical hearing aid this trial is necessary for some deaf patients especially those who have been deaf for a long time; in fact some patients can never get accustomed to a hearing aid, because it amplifies all sounds and therefore makes hearing uncomfortable to a person who has been shut out from noise for a long period.

*Deafness Clinic.*—Under the auspices of the Medical Research Council a Deafness Clinic was instituted in Queen Square Hospital, London. This clinic was really a research centre for electrical hearing aids. Much work was done there and useful information obtained. This deafness clinic might be taken as an example of what must be done in every centre.

In future it must be the duty of the Otological Departments of the central hospitals in each region not only to treat diseases of the ear but also to aid its diminishing function. These departments would have in fact a tripartite duty. They would be concerned with (1) treatment of diseases of the ear, (2) treatment of deafness by expectant measures such as removal of any septic foci; improvement of the aeration of the middle ear; or by direct operation such as fenestration if the results of this operation warrant its continuance; (3) giving advice on the use of a suitable hearing aid and also advice on the educational and sociological training of the deaf.

Where hospitals are in close proximity this third rôle might be delegated to a single deafness clinic where patients could be referred for advice on, and if necessary the fitting of, a suitable hearing aid. The sociological aspect of this clinic would have to be emphasised. Advice could be given on lip-reading and on the possibility of congenial employment.

These three duties overlap. Every case of otitis media coming



to the Ear, Nose and Throat Department has the hearing tested, every case of progressive middle-ear catarrh or otosclerosis has a full range of hearing charted along with an audiometric test.

However a deafness clinic means more than this and we are hoping to have such a clinic functioning whenever material is available.

### TESTING FOR HEARING AIDS

At the Deafness Clinic in Queen Square Hospital patients who have had the ears examined, an audiometric test done, the type of deafness diagnosed, are tested with actual spoken words—groups of words have been chosen of single syllables without any correlation. These are transmitted to the patient by gramophone records through an amplifier and loud speaker, but varying the amplification so that the patient can be tested theoretically at different levels of speech without altering the position.

Ordinary speech in a quiet room reaches the human ear at a level varying from 30 to 60 decibels making an average of 45 decibels above the normal threshold, though it should be well understood at 15 decibels below this, although this depends on the surrounding noise. With normal hearing the voice is unconsciously raised to about 10 to 25 decibels above the level of background noise. (A decibel is the unit of intensity of sound, 10 decibels corresponding to a tenfold increase in sound intensity, 20 decibels to a hundredfold increase. A loud voice in a quiet room reaches the ear at about 60 decibels amplification—that is about a millionfold increase in sound intensity.)

A patient listens to and repeats the groups of words on the records but at different amplifications. The percentage of the hearing can thus be charted and a graph obtained. It is curious that if sentences are used instead of single words it gives a remarkably different graph, varying, of course, with the intelligibility of the patient. It is for this reason that single words have been chosen for the test. A 40 per cent. level of word recognition was taken as a critical level. For instance, a person might have no difficulty with a loud conversation voice and yet have total deafness at church level and a slight difficulty with the ordinary conversation voice. During the test the patient sits in front of the loud speaker with his ear against a frame (at a given distance from the loud speaker—this distance of course has to be measured out by means of an artificial ear to get the proper amplification readings). After the test the patient moves away from the loud speaker and is fitted with various types of hearing aids—the microphone of the hearing aid replacing the patient's ear in the aperture in front of the loud speaker while the patient listens through the ear-piece in comfort. The tests are repeated with, of course, a different series of words and a percentage recognition of the words charted. The alteration in the graph can be seen easily and the

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graph showing the nearest reading to the patient's original graph is taken as the most suitable hearing aid for the patient. One finds in many cases that the hearing aid does not improve the patient's hearing sufficiently to hear at church level or the ordinary conversation voice, while it is usual that the loud voice can be brought up. In such a case no electrical hearing aid would be recommended because a non-electrical aid would be sufficient to allow the patient to hear a loud conversation voice possibly with less distortion than the electrical aid.

To allow a deaf person to hear in a theatre or at a concert a different method is advisable. An amplifier picks up all sounds and the closer the sound is to the microphone the louder that sound must appear to the deaf person. If a deaf person uses an ordinary amplifier in a church or theatre with the intensity of amplification turned to the speaker or orchestra with all other sounds cut out all would be well, but if his next-door neighbour coughed or moved in his chair that noise would be so intensified by the amplification that it would cut out all other sounds. Consequently it has been suggested that the hall or theatre is fitted with a microphone and an amplifier such as is used for a loud speaker, but the loud speaker is replaced by a wire which extends all round the hall. A deaf person using his own aid but with the microphone removed and replaced by an induction coil would then pick up what is being delivered to the microphone in the pulpit or on the stage without distortion of the surrounding sounds.

Much research work has still to be done and little headway can be made until further deafness clinics are established. The equipment for such a clinic is rather difficult to obtain but we are hoping that the Ministry of Supply may help with this.

The testing of hearing is a wearisome business, but much of it could be done by the technicians under the supervision of an otologist who must decide whether the patient should be allowed to use a hearing aid of the electrical type or whether he would benefit by a non-electrical instrument.

#### NINE COMMANDMENTS FOR THE DEAF

The deaf public must be re-educated to be less self-conscious of their disability and thereby not try to conceal their deafness.

Berry of Harvard Medical School gives nine commandments for the "hard of hearing" which might be quoted:—

- I. Thou shalt frankly confess thy deafness to thyself and before thy fellow men. Let there be no deceit or false pride.
- II. Thou shalt not covet thy neighbour's hearing, but shall rejoice that thou livest in an age when thy handicap can be made so small.
- III. Early and again shalt thou consult thy otologist and accept every scientific aid he can render.

- IV. Eschew the quack and his devices. Easy and broad is the way to his door and many there be that find it.
- V. Thou shalt join and work for a league for the hard of hearing where thou wilt receive encouragement and stimulation for thyself and wilt find happiness in serving thy brother.
- VI. So love thy neighbour that thou do everything in thy power to help him when he would have speech with you. To this end :
- VII. Thou shalt study lip-reading in season and out of season.
- VIII. Thou shalt secure and use the best ear phone thou canst discover.
- IX. Triumphantly shalt thou rise above thy infirmity, and so conduct thy life that the world hath need of thee.

### THE DEAF CHILD

I have purposely refrained from talking about the problem of the deaf child. I have tried to limit myself as much as possible to the deaf adult, but I must refer for a moment to the problem of the education of the deaf which of course starts with the child.

A further committee of the Medical Research Council is discussing this subject.

For the deaf-mute there must be only educative measures, teachers of lip-reading to teach him to speak and communicate with others even in a toneless voice. For those with islands of hearing a certain amount of education can be obtained by the use of an amplifier and the hard of hearing can be taught to lip-read and to use, if necessary, an amplifier. Special classes can be fitted with a microphone, an amplifier and multiple ear phones, and different circuits can be tapped so as to give different degrees of amplification.

Visiting the clinic in Manchester under the Ewings makes one realise how little we are doing in our centres.

Finance has always been a difficulty. Those of us who have been experimenting with hearing aids have had to do so at our own expense. However these days are passing, clinics will be opening, I hope, everywhere so that the otologist can be blamed no longer for not trying to treat the function of the ear, and patients will not have to be bullied by first class advertisements and first class showmen into buying instruments which will prove useless and even detrimental.

## THE OPERATIVE TREATMENT OF NON-SUPPURATIVE MIDDLE-EAR DEAFNESS \*

By I. SIMSON HALL, F.R.C.S.Ed.

ALTHOUGH greatly publicised of late this is no new procedure, and the operation as practised at present was first performed in principle by Jenkins of London in 1913. Advances since that date have been chiefly technical and instrumental, and the pioneer in this field is Professor Holmgren of Stockholm. From him workers in America and in this country received the stimulus which prompted their own researches.

The operation has now reached a point in development when the patient need no longer be told that he is the subject of experiment, but can be given a reasonably accurate idea of the chances of obtaining relief from his deafness, and the probable extent of the relief.

The first part of the operation is the provision of access to the labyrinth, and this closely resembles the modified radical mastoid operation. The part which the operator wishes to expose is the ampullary end of the horizontal semicircular canal, where the new opening is cut, which is to replace the immobilised oval window.

An elaborate outfit is required for this part of the operation, and it includes a dental drill, continuous irrigation and suction apparatus, and a dissecting microscope to provide magnification. This last piece of apparatus is perhaps the most important as the delicate manipulations required to cut an opening measured in millimetres are impossible without adequate enlargement of the field.

The duration of the operation is now on the average about an hour and a half, though in unfavourable cases it may be much longer. The great reduction in time from the earlier operations has been made possible by experience, for this is essentially a team job. Of the members the anæsthetist has it in his power to make or mar the operation, and he has to realise that immobility, hæmostasis and elasticity in operating time are essential. We have found that continuous pentothal, reinforced as required, or cyclopropane, are the most useful forms of anæsthesia.

After operation there is discomfort from labyrinthine irritation for three or four days. This is the usual giddiness, some sickness, and a variable degree of inco-ordination and loss of accommodation. There is rarely any pain at any stage, and this is frequently a source of surprise to the patient. The hearing shows a dramatic improvement

\* Read at a meeting of the Edinburgh Medico-Chirurgical Society on 5th June 1946.

immediately after operation, and it is one of the most fascinating points about this procedure that one can judge success or failure even during the operation if it is performed under local anæsthesia. The patients have to be warned, however, that this improvement will be lost for a time after two or three days. The hearing comes back in fourteen days or so, and goes on improving till the ear is completely healed, when it is usually at its highest level. It is this fact that renders complete treatment to the point of healing important, as the moist discharging cavity rarely gives a good result.

The selection of suitable patients is of the utmost importance if good results are to be obtained. This operation is applicable primarily to young people, preferably under thirty years, but good results have been obtained by the writer up to the age of fifty-six. While it is the treatment of choice in those who are young and not too deaf, great care and considerable experience is required in selecting the older patients.

As the operation can only raise hearing by a fixed amount—30 decibels—if the patient is so deaf that this improvement will not raise the hearing into the region of normal then there is rarely any purpose in operating. If, therefore, the patient requires to be spoken to in a very loud voice the probability is that the time for operation is past.

There are certain conditions which are contra-indications to operation. Of these nerve deafness is one of the most important. Patients who have been deaf all their lives, who have developed nerve deafness through injury or disease, or who suffer from the nerve deafness which is the usual accompaniment of advancing years, are also unsuitable. Suppurative conditions of the ear for the most part prevent a successful result, and active discharge or the presence of scars and adhesions in the middle ear usually preclude any benefit.

In judging these patients we have to take into consideration not only the type of deafness and its degree, but also the factors which have led the patient to seek advice. These may be economic or psychological in that the patient is unable to earn a living or to take up some chosen line of work, or that they feel the burden of deafness so severe that life becomes unbearable. Or again, patients may come for treatment so that they may re-establish social contacts or because deafness is proving a domestic nuisance. Naturally the urgency of such cases as these last is very much less as compared with those where deafness is a severe economic handicap, and in giving advice to patients these aspects and the chances of success in the particular case have to be carefully balanced. For instance, if a man were faced with unemployment because of increasing deafness, one would be inclined to advise operation even though the chances were only one in two of obtaining a good result, where the same proportion of chance would negative the patient who required improvement in hearing merely as a social amenity.

The results which can be obtained from this operation can be stated roughly as an improvement in approximately 80-85 per cent. of the class of case regarded as the most favourable. As age increases and favourable subjects become fewer the percentage chance of success drops sharply, until at forty years of age 60-65 per cent. is probably a reasonable estimate of success.

In undertaking this operation it must be clearly realised that it is a major operation and entails a considerable amount of time for convalescence, and although complications have been few, they have been of rare occurrence chiefly because of the very great care in the development of this operation, and it does not mean that the same high percentage of safety will be maintained if there is laxity of technique or inexperience in its performance. It must be impressed, therefore, upon the patient that all the dangers attending a major operation are present. In the series of cases on which these remarks are made there have been no cases of labyrinthitis, and one case only of facial paralysis which recovered in about four weeks after the operation.

It is noteworthy that fully half the patients at present upon the waiting list are there on the recommendation of their friends. This is an encouraging feature, for the fact that they are willing to undergo this operation for the benefits they have observed in others, shows that the patients at least are convinced that the operation is worth while. After all, this is the only treatment which restores hearing to these patients.

#### DISCUSSION

*Dr Douglas Guthrie*, in congratulating the speakers on their contribution to a most important problem in otology, enquired whether the alleged recent increase in deafness was based upon statistical evidence and to what extent it was due to the greater number of elderly persons now living. The solutions of the problem offered by *Dr Martin* and *Dr Hall* were admittedly palliative, and dealt with the results of deafness rather than the causes. The cause of otosclerosis, probably the commonest type of deafness, remained unknown, and there was great need for further research in the pathology and biochemistry of this disease. It seemed desirable that some of the younger otologists should continue the work so admirably initiated by the late *Dr J. S. Fraser*. The technique was tedious but the field was full of promise. Viewing the problem from the national point of view, *Dr Martin's* solution was of great value. A cheap and suitable hearing aid was much to be desired, and hearing aid clinics were essential to accurate prescribing. The operation advised by *Dr Hall* was limited in its applicability, and even if it could be proved to be safe and successful in every case it demanded great technical skill and much time, so that it could deal with only a very limited proportion of the large number of deaf persons. Were it possible to devise a simpler means of constructing the new window, the operation would naturally have a wider field of usefulness.

*Dr Ogilvie* was of the opinion that the success of the operation depended on maintaining the patency of the opening in the wall of the middle ear by plugging with cartilage. It was interesting to note that in this connection



two workers in Glasgow had implanted portions of liver, spleen, muscle, cornea and cartilage subcutaneously in animals and had found that at the end of three weeks all of these tissues had disappeared except cornea and cartilage. Both of these substances are translucent and are apparently able to maintain their existence as homografts by reason of their high content of mucoprotein.

*Dr Stewart* said that, when a patient came for a consultation and was desirous of knowing about the operation under discussion for the alleviation of deafness, he wished to know exactly what he was in for and what were the risks. He would want to know first of all whether the operation might have a fatal result. Again he would wish to know whether, if the hearing were not improved by operation, could it be made worse or might he lose his hearing altogether.

*Dr Lumsden* and *Dr Wilkie Millar* also spoke.

*Dr Hall*, replying to the question regarding mortality rate, said that there had been two deaths in the series ; one of acute cardiac collapse after operation had been completed, and the other as a result of morphine poisoning in a patient who had previously had an acute poisoning following an operation under local anæsthesia. It could therefore be said that this operation is not one without risk, and that there are the same risks as are associated with any major surgical operation, but such accidents as have occurred cannot be considered as having been due to the operation itself.

*Dr Hall* also thanked *Dr Ogilvie* for his interesting suggestion regarding materials which were not absorbed, and said that he would look into this question immediately.

## PERIARTERITIS NODOSA \*

*Presentation of Case.*—A man, aged 24, was admitted on the 25th September 1946 with a diagnosis of acute rheumatism. He gave a past history of measles and whooping cough as a child, and of an attack of mild jaundice four years ago.

Three weeks before admission he had complained of general malaise, nausea and fever. Soon afterwards he noticed pains in the shoulder joints, across the back and in the muscles of his limbs. After three days the pains left the shoulder joints and affected his elbows. After ten days all the pains passed off and he got up, but felt so weak that he had to return to bed. There was never any swelling or redness of the affected joints. His urine had been dark for a week before admission, and he had noticed a dry cough for about the same time.

*On Admission.*—He was extremely pale, with a moist skin tinged with jaundice. Temperature 98° F., pulse rate 120, respiratory rate 20. There were no joint pains or swellings. His blood pressure was 210/135, but there was no evidence of cardiac hypertrophy or of valvular damage. Scattered crepitations were to be heard throughout both lung fields. Spleen and liver were not enlarged.

*Investigations.*—Urine sp. gr. 1022, albumen++, red blood cells++, many epithelial, granular and red cell casts. Blood sedimentation rate 27 mm. in first hour (Westergren). Icteric index 26.9. Van den bergh—indirect positive. Red cell fragility normal. Bleeding time four minutes. Blood culture negative. Wasserman reaction negative. Auto-hæmolysins not present in blood. Blood urea nitrogen 31.9 mg. per cent. Plasma albumen 2.18 g. per cent. Plasma globulin 2.23 g. per cent.

*Blood Counts*

Date.	Red Cells.	Hæmoglobin.	White Cells.	C.I.	Eosinophils.	Reticulocytes.
25.9	...	75 per cent.	12,000	...	...	...
30.9	2,600,000	40 "	26,000	0.7	1 per cent.	...
1.10	...	...	20,000	...	...	...
7.10	1,960,000	40 per cent.	27,800	1.0	5 per cent.	38 per cent.
10.10	2,300,000	60 "	17,000	1.3	...	13 "
12.10	2,260,000	52 "	12,200	1.2	...	13 "
14.10	...	50 "	...	...	...	10 "
16.10	...	50 "	...	...	...	...

*Treatment.*—Salicylates, iron by mouth, and liver extracts by injection. Two pints of blood were transfused on the 7th October, and three pints on the 16th October.

\* A Clinico-Pathological Exercise held in the Pathology Lecture Theatre, University of Edinburgh, on the 30th November 1946.

*Course.*—His temperature remained normal throughout the illness except for an occasional evening rise to  $99.5^{\circ}$  F., but a fast pulse rate persisted. His blood pressure never fell below 200/120. On the 27th September, œdema of the orbital tissues and conjunctivæ occurred. He complained of dim vision, and papilloedema was also observed. By the 30th September the jaundice was fading, but he now had a complete loss of vision in the right eye due to a retinal detachment. Another retinal detachment of his left eye occurred on the 7th October. A mitral systolic murmur developed, and he continued to pass urine containing large quantities of red blood cells, pus cells and casts.

In spite of treatment his condition steadily deteriorated, the two blood transfusions resulting in but transient benefit to his general condition and blood picture. The specific gravity of his urine gradually fell and he died on the 16th October.

*Ward Diagnosis.*—Nephritis and hæmolytic anæmia.

DR GIRDWOOD.—We seem to be dealing here with a generalised condition, the main features of which are renal damage, hypertension, non-obstructive jaundice and anæmia.

I do not think that we need waste time discussing acute rheumatism. The possibilities of septicæmia, bacterial endocarditis, or of Weil's disease require mention, but not one of these conditions really fits in with the picture described.

Considering the case from the renal angle, I would exclude malignant hypertension because of the anæmia and the jaundice, and an acute flare-up of a chronic nephritis for the same reason.

The reticulocyte response is such as to rule out a toxic form of anæmia. I would say that it cannot be hæmorrhagic either, for, in the absence of any gross bleeding, the hæmoglobin fell from 75 to 40 per cent. in five days. I feel that the peak reticulocyte count rules out both an iron-deficiency anæmia treated with iron at the 40 per cent. HbO level, and even a pernicious anæmia at the two million level, treated with liver. I would, therefore, label this a hæmolytic anæmia. Other features of the case do not fit a diagnosis of paroxysmal or nocturnal hæmoglobinuria, congenital hæmolytic anæmia, or Lederer's anæmia. Infections, poisons and allergy can give rise to a hæmolytic anæmia. Then we have the group of acquired hæmolytic anæmias, a vague, unsatisfactory group, but in it some include the symptomatic hæmolytic anæmias.

I feel that in dealing with this latter class, we are getting near the diagnosis in this case. The group includes cases of hæmolytic anæmia, with reticulocytosis, with an indirect positive van den bergh reaction, with urobilinogenuria, and with a crisis as in the patient presented to-day. Such a hæmolytic anæmia may be symptomatic of a number of conditions, including leukæmia, cancer, liver damage and pneumonia. A rare cause is disseminated lupus erythematosus. This disease is variable in its onset. There may be abdominal pain, nausea, rheumatic pains, weakness and fever. Albuminuria is

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*References:—Shortage of space precludes full documentation which may be obtained on application to Clinical Research, Dept. S. J.*



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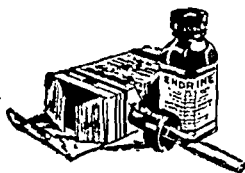
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quite usual, with casts and red cells in the urine. There is not generally a leucocytosis. The cutaneous symptoms may be superimposed on an obvious chronic lupus erythematosus, or may be acute from the onset. Sometimes the rash subsides and there may be no signs of it at death. This diagnosis would explain many of the features of the case, but there is no history of a rash and a leucocytosis is not usual.

Now, one point that struck me on reading the blood figure was a 5 per cent. eosinophilia with a white cell count of 27,800. This, and certain other features, at once suggested the diagnosis of periarteritis nodosa.

The clinical features of this disease, thought by many to be allergic in nature, include fever, leucocytosis, albuminuria, vague pains, hypertension, visual disturbances, icterus and eosinophilia. The details of the type of anæmia present in this condition are uncertain because of the inexact methods of recording in many of the case histories. I think it is very likely that hæmolytic anæmia may occur in this condition, just as in acute disseminated lupus erythematosus.

*Dr Girdwood's Diagnosis.*—Periarteritis nodosa.

*Anatomical Diagnosis.*—Periarteritis nodosa combined with acute rheumatism.

DR CAMPBELL.—Three conditions were suggested by the post-mortem findings—a combination of acute rheumatism with periarteritis nodosa, Libman-Sacks disease and malignant hypertension. The heart was enlarged (weight 400 grams) through slight general dilatation and considerable left ventricular hypertrophy. The mitral valve showed an early verrucose endocarditis, with vegetations confined to the line of closure. There were no macroscopic stigmata of previous rheumatism. Microscopically, areas of acute myocarditis in ventricular and auricular (septal) muscle, showing infiltration by neutrophils, lymphocytes, histiocytes, and eosinophils were present, with extension of a similar inflammatory reaction to the overlying auricular endocardium. No Aschoff bodies were seen. There was a diffuse valvulitis of the mitral cusps, mainly lymphocytic in character, with a few eosinophil cells, the vegetations being compact with no visible bacteria. There was extensive vascularisation of the cusps, with well formed arterioles, suggesting former rheumatic endocarditis.

The lungs showed œdema and chronic venous congestion. Microscopic foci of fibrinous alveolar exudate with fibrinoid thrombosis and necrosis of alveolar capillaries, compatible with an early rheumatic pneumonia, were present.

The kidneys were slightly enlarged (230 and 215 grams) and the cortices were stippled with petechiæ. A few recent infarcts were present, with macroscopic thromboses of several arcuate arteries. Histologically, extensive fibrinoid necrosis of afferent arterioles, often extending into the glomerular capillaries, was seen. Some glomeruli also showed endothelial proliferation, leucocytic infiltration, and

occasional capsular epithelial crescents. Some arcuate arteries showed thromboses with segmental destruction of the internal elastic lamina and media together with recent replacement fibrosis, as seen in the subacute lesions of periarteritis nodosa. No old arteriosclerotic changes were seen.

The spleen was slightly enlarged, with one large recent infarct.

The upper jejunum showed several small areas of congestion, hæmorrhage and early necrosis of mucosa. Microscopically these revealed thromboses of both arterioles and venules, with patchy fibrinoid infiltration of their walls, and a considerable fibroblastic proliferation, with surrounding lymphocytic and eosinophilic infiltration.

The liver showed cloudy swelling. A single small vessel—either an artery or portal vein—was found thrombosed, and microscopically a picture like that of subacute periarteritis nodosa was found, as in the kidney.

The bone marrow showed a marked hæmopoietic reaction, predominantly normoblastic in character.

Although the kidney picture suggests malignant hypertension, the periarteritis of the larger arteries, the endocarditis and the myocarditis are against this diagnosis.

The combination of verrucose endocarditis, myocarditis and widespread inflammatory and necrotising lesions of arteries and arterioles is at first sight very suggestive of Libman-Sacks disease; the absence of skin lesions by no means eliminates this possibility.

The distribution of the endocardial vegetations, however, is much more suggestive of acute rheumatism, and the acute myocarditis is fully compatible with the latter diagnosis, in spite of the absence of Aschoff bodies.

The arterial changes are very suggestive of periarteritis nodosa, and the diagnosis would therefore appear to be acute rheumatism combined with periarteritis nodosa, a combination described by Friedberg and Gross among others, and analogous to the combination of lesions produced by Rich and Gregory in rabbits. The eosinophilia seen in some of the lesions would agree with such an allergic syndrome.

The bone marrow findings were compatible with a hæmolytic anæmia. This would be, as Dr Girdwood suggests, a symptomatic phenomenon, secondary to the rheumatic process.

DR GLAZEBROOK.—We are grateful to Dr Girdwood for his ingenuity in arriving at a diagnosis, and to Dr Campbell for demonstrating the autopsy findings so thoroughly. It recalls the last case presented at these clinico-pathological meetings, of a rheumatic pneumonia with a hæmorrhagic nephritis, and illustrates how closely the phenomena of acute rheumatism and of periarteritis nodosa are linked. Both conditions are probably the result of widespread vascular damage produced by allergy, and as Dr Girdwood has said, allergy can bring about a hæmolytic anæmia. One feels that the kidney changes of malignant hypertension were secondary to the periarteritis

# SOME PRACTICAL CONSIDERATIONS IN THE SURGERY OF THE HAND AND FINGERS \*

By ERIC L. FARQUHARSON, M.D., F.R.C.S.Ed. and Eng.

INJURIES of the hand and fingers head the list of industrial accidents, and infections form a large proportion of the cases treated in our out-patient departments. When we realise the importance of our hands and fingers to each and every one of us, we must admit that, in our teaching and practice, the treatment of hand conditions does not receive the attention it deserves.

This branch of surgery is an unusually wide one, and I will attempt no more than to discuss certain practical considerations, which may help us as general surgeons and general practitioners in the cases which we are called upon to treat.

Any injury, infection or other disease of the hand presents a problem which is essentially one of anatomy. Without a thorough knowledge of the anatomy of the part, the surgeon cannot estimate the damage that may have resulted from an injury, nor can he determine the methods which are best suited to its repair; he cannot visualise the exact location of an infective process, or the directions in which it may spread, and he cannot with safety plan his incisions for drainage. It is my intention therefore to discuss with you to-day a few of the more important anatomical features, which I believe to be of essential and far-reaching importance in treatment.

**THE TERMINAL PULP OF THE FINGER.**—The soft pad of tissue covering the front of the terminal phalanx is composed of subcutaneous fat which presents a very specialised arrangement. It is subdivided into fifteen to twenty compartments by fibrous septa which are attached both to the skin and to the periosteum of the phalanx. These compartments run in the long axis of the finger, and are limited proximally by a process of the investing layer of deep fascia which is attached to the base of the phalanx at the level of the insertion of the long flexor tendon. The distal four-fifths of the pulp consists therefore of a closed space or series of closed spaces. The shaft and the distal end of the phalanx derive their blood supply from branches of the digital arteries passing through the closed space. The base of the phalanx, on the other hand, is supplied by separate branches which do not traverse this space.

This specialised arrangement has an important bearing on the localisation and spread of pulp infections and on their treatment.

\* A Honyman Gillespie Lecture given in the Royal Infirmary, Edinburgh, on 14th March 1946.



The strong proximal boundary of the fascial compartment acts as an effective barrier to infection spreading up the finger towards the palm; it tends rather to spread dorsally round the sides of the nail bed, and so to give rise to a collection of pus beneath the nail. The infection is therefore likely to remain localised to the distal segment of the finger. The advantages of such localisation, however, are offset by the considerable danger of necrosis of bone. This is now recognised to be due to the cutting off of the blood supply, and not to a direct spread of the infection. The base of the phalanx is usually unaffected; it is the shaft and the distal end that are involved—the parts which are supplied by vessels traversing the closed compartment. These vessels are in danger of becoming thrombosed or occluded at an early stage of the infection, owing to the increased tension which is produced.

In view of the danger of necrosis of bone, early diagnosis of a pulp infection is of the greatest importance. There should never be any question of waiting till fluctuation has occurred. It is enough that the finger tip is swollen and indurated, and that the patient is suffering from throbbing pain. If incision and drainage are delayed until there are more definite signs of abscess formation, it is likely that the finger tip will be no more than a bag of pus, and that the distal part of the phalanx will already have undergone necrosis. The rapidity with which the condition may develop is not generally recognised. It is possible for advanced bone necrosis to have occurred within forty-eight hours of the onset of symptoms.

It is now generally agreed that an abscess in the finger pulp should always be opened from the lateral side. An incision in the mid-line of the pulp is contra-indicated for several reasons. Such an incision provides imperfect drainage, because it may open no more than one of the longitudinal compartments, it destroys the sensitivity of the pulp in the area where it is most highly developed (at the central loop or whorl), and it may result in the opening and consequent infection of the flexor tendon sheath. A lateral incision should therefore be employed in every case; it is carried down to the bone, and the knife is made to pass in front of the bone, so that most at least of the radiating fascial trabeculæ are divided. The closed space is then well opened-up by the blades of a small hæmostat; and a rubber tissue drain is introduced. If a radiograph has shown any infection of the bone, it is better to insert a small gauze pack; this ensures better drainage, and prevents too rapid healing of the wound.

When a large abscess is encountered, it is an advantage to make a second incision on the opposite side of the finger, so that through-and-through drainage can be provided by a strip of rubber passed completely across the pulp in front of the phalanx. Care should be taken that the channel is of equal width throughout, and that it is not narrowed in its middle part.

The so-called "fish-mouth" incision, made by joining the two lateral incisions round the tip of the finger is not now advised, except

for very severe infections. It has no advantages in the average case, and is liable to leave an unsightly deformity.

**THE WEB SPACES.**—A subcutaneous infection of the palmar aspect of a finger cannot spread directly upwards into the palm, because of the attachment of the skin to the fibrous sheath at the level of the proximal crease. This barrier exists however only across the front of the finger, and the infective process has only to turn slightly to the side into the web space in order to find its upward spread quite unimpeded.

The web spaces are bounded on each side by the digital slips of the palmar aponeurosis, which fuse with the fibrous sheaths. Each space is occupied by loose connective tissue and fat, and is partially divided by the transverse ligament of the palm, which binds together the heads of the medial four metacarpals. The larger anterior part of each web space contains the lumbrical muscles and the digital vessels and nerves; the smaller posterior part contains the interosseous muscle. Distally, each web space is continuous with the loose connective tissue on the sides of the fingers. Proximally, it communicates, by way of the fascial compartments containing the lumbrical muscles (the so-called "lumbrical canals"), with the deep spaces of the palm.

Infection of a web space occurs most commonly as a result of spread from a subcutaneous infection of the proximal two-thirds of a finger. It may result also from a thecal infection, especially of the index, middle or ring fingers, in which the tendon sheaths, having no continuation into the palm, may rupture into the web spaces. Occasionally it develops from a direct inoculation of an overlying wound (*e.g.* a septic blister).

A web space infection offers no difficulty in diagnosis. The web becomes red and swollen, both towards the palm and the dorsum, and the adjacent fingers are seen to be pushed apart by the swelling. The infection, which begins usually in the anterior part of the space, tends to spread to the dorsal part, where it may point under the thinner skin in this situation. Fortunately, spread up the lumbrical canals to the deep palmar spaces does not occur as a general rule until the later stages of the infection, but the danger of such a serious complication demands that early incision and drainage should be carried out.

The placing of drainage incisions depends upon the conditions present. If an abscess is pointing in any particular situation it is obvious that the incision should be made in the overlying skin. In the absence of such localisation it is probably advisable that the incision should be placed on the dorsal surface of the web. When the web infection is obviously due to extension of a finger infection the lateral side of the finger should be laid open at the same time, as in the approach advised by Iselin. When the anterior part of the web is extensively involved the incision may be carried over the free margin of the web on to the anterior surface. Through-and-through drainage by separate anterior and posterior incisions has nothing to

commend it; it may cause damage to the lumbrical muscles or to the digital vessels and nerves. If it is suspected that spread has occurred to the deep palmar spaces, the lumbrical canal should be gently explored with a sinus forceps; should pus be located, a sheet rubber drain may be left *in situ*, or a more direct approach to the space (that of Henry) may be carried out.

**THE METACARPO-PHALANGEAL JOINTS.**—The collateral ligaments, which strengthen the capsule of each metacarpo-phalangeal joint, must be regarded as among the most important structures in the hand. They are attached proximally to the sides of the metacarpal head in its narrow posterior part; owing to the direction of their fibres and to the shape of the metacarpal head, they are relaxed when the joint is extended, but are completely taut in the flexed position. Thus when the fingers are held straight, they can be abducted and adducted with ease, but when they are flexed at a right angle to the palm, no such movements are possible.

These anatomical considerations have an important bearing on treatment, for, if the collateral ligaments are allowed to become shortened, it is then impossible for the phalanx to sweep round the curve of the metacarpal head, so that the finger becomes fixed in extension. It is justifiable therefore to make it an absolute rule that except after suture of a divided extensor tendon, *a finger should never be immobilised in extension at the metacarpo-phalangeal joint.*

Most authorities at the present time agree in condemning any attempt at forcible manipulation of stiff fingers. It is pointed out that such treatment causes minute lacerations in the ligaments, rather than true stretching, that such tears will be repaired by fibrosis, and that a still greater degree of contracture will be the only result achieved. It is my own view however that forcible manipulation is sometime successful, and may therefore be justified in the case of stiffness at the metacarpo-phalangeal joints. There is however one important condition. After the manipulation, full flexion must be maintained by a plaster splint applied over the dorsum of the hand and fingers. The immobilisation is maintained without interruption for at least seven to ten days, so that the collateral ligaments may become reorganised in the stretched state. I can recall at least six cases where disability was due to one or more fingers having become stiffened in extension at the metacarpo-phalangeal joints, and which I ventured to treat in this way. In four of these cases there was no doubt that the manipulation resulted in a considerably increased range of movement. In the other two cases the benefits were doubtful, but I am convinced that their condition was not made worse.

It should be noted that the heads of the metacarpals do not lie in the same plane; there is a metacarpal arch in the hand, more marked and more important than the metatarsal arch in the foot. Because of this arch, the planes of flexion of the fingers are not parallel. The fingers normally spread widely as the hand opens, but the

converge strongly and cannot voluntarily be separated, as the hand closes. Each finger, when flexed individually, points towards the tubercle of the scaphoid. It is most important therefore that when a finger is immobilised its correct plane of flexion should be maintained.

**THE LUMBRICAL AND INTEROSSEOUS MUSCLES.**—The lumbricals and interossei, along with other intrinsic muscles, have great functional importance in promoting the muscular balance of the hand as a whole. Their actions under normal conditions are well recognised, but the effects which they may produce in the presence of fractures or other abnormal conditions are less generally understood.

In fractures of the metacarpals and phalanges, the lumbrical and interosseous muscles are largely responsible for the deformity that ensues. It should be noted that these muscles are anterior to the plane of the metacarpals, but posterior to the plane of the phalanges, so that the opposite type of deformity is produced in the two cases.

In fractures of the shaft and neck of a metacarpal, the head of the bone is usually bent towards the palm, so that an angle pointing dorsally is formed. In the case of the second, third and fourth metacarpals the deformity is increased by the action of the extensores carpi, which draw the proximal fragments into extension. All the muscles producing the deformity are relaxed by placing the wrist in dorsi-flexion, and the metacarpo-phalangeal joints in flexion. With the hand in this position an unpadded plaster cast is applied and is moulded closely against the dorsum of the hand. The old method of the "closed-fist bandage" has nothing to commend it, for existing angulation is likely to be increased, and all the fingers are needlessly immobilised. In spiral fractures of the metacarpal shafts, slight over-riding may be present, and continuous traction may then be considered necessary. For the reasons already given, it is essential that such traction should be applied with the fingers flexed; traction in the old-fashioned "banjo" splint must be absolutely condemned.

In fractures of the first and second phalanges the head of the bone is bent backwards, so that the angle points towards the anterior surface. Because of this deformity, and quite apart from considerations referable to the metacarpo-phalangeal joints, a fractured finger should always be immobilised in flexion. If continuous traction is necessary it too must be applied with the fingers flexed.

**TENDON SHEATHS AND PALMAR SPACES.**—The anatomy of the tendon sheaths of the fingers and thumb, their extensions into the palm (the radial and ulnar bursæ), and the deep fascial spaces of the palm (the thenar and middle palmar spaces) presents a wide field for discussion, into which it is impossible for us to enter in the time at our disposal this afternoon, but the general arrangement is well known.

Teno-synovitis is of course a most serious condition, and demands early diagnosis and drainage. In the index, middle and ring fingers, the digital sheaths end at about the level of the metacarpo-phalangeal joints. The proximal end or *cul de sac* of the sheath is the part in

*function.*—A fractured finger must be immobilised in flexion, and the thumb in opposition, that is, in the position for grasping a tumbler. In the case of infections, drainage incisions should be planned and dressings applied so that the position of function may be maintained in after-treatment. The immobilising effect of dressings and bandages must be recognised. Flexion of the fingers, especially at the metacarpophalangeal joints, should be maintained by a splint or a plaster cast, and in the same way, the thumb must be kept in opposition. The septic hand, protected only by bandages, must not be allowed to lie with its palmar surface resting against the trunk, for the thumb will then be pressed backwards into the plane of the fingers, and irreparable damage may be done.

(4) *Active movements of all unaffected fingers must be carried out.*—In fractures of the wrist, carpus and metacarpus, the fingers should be left with an unrestricted range of movement. In such cases, the plaster cast must not cover the palm beyond the flexion creases, in order to allow full flexion at the metacarpophalangeal joints. To ensure this these joints should be passively flexed to 90° while the plaster in the palm is still soft. The metacarpal bone of the thumb, unless it requires to be immobilised, must be left with the power of full opposition. If one finger requires to be immobilised the other fingers should be left with a full range of movement. Active movement of the unaffected fingers must not only be allowed—it must be insisted upon. For the best results to be obtained the movements must be purposeful and co-ordinated, and the limb as a whole should be kept in use as far as possible.

I have vivid recollections of a surgeon in Edinburgh who some years ago had a serious infection of finger, hand and forearm. There were many of us who thought that the subsequent disability, which we believed to be inevitable, would preclude any further operative work. But, as soon as the acute infection had subsided, that surgeon worked at the fingers during every hour of the day, and to my knowledge during many hours of the night, with the result that, after three or four months, the hand had completely regained its function.

It is rare indeed that we meet such co-operation on the part of the patient—at least in hospital practice. We must admit however that the fault lies partly at our own door. How often do we tell the patient, somewhat casually and with no special emphasis, that he should move his fingers, and then forget all about him until he reports again—perhaps two or three weeks later?

Every patient, from the casual labourer to the skilled craftsman, is surely fully conscious of the vital importance of his hands for his very livelihood. His apparent lack of co-operation is, I believe, due to his ignorance of the seriousness of his condition in regard to its effects on his earning capacity. He should be warned that in many ways a compound fracture of a finger has more serious implications than a compound fracture of the femur, and that a bad septic hand

is more to be feared than a gangrenous appendicitis. He should certainly be told that the only really effective way of restoring function to his hand lies in the active exercises which *he alone* can carry out. He must be told that "exercises" do not consist of mere aimless widdling of the fingers, but that he must use his hand for all possible purposes. It should be impressed upon him that such treatment is many times more important than anything that the hospital can provide in the way of massage, radiant heat, electrical treatment, etc.—these things in which he now has such touching and such unfounded faith.

Much wonderful work has been done on the reconstructive surgery of the hand. Stiffened fingers may be mobilised and their function restored. Skin, tendons, nerves and even bones may be transplanted from other parts of the body, so that whole fingers may be reconstructed. At best, however, and even in the hands of those who have the most experience, the results are somewhat uncertain, and the complexity of the operations required necessitates many months of incapacity, which the patient can seldom afford.

We believe that many of the disabilities which are the end results of injury or infection could be prevented by early correct treatment, and by the co-operation of the patient. It is along these lines therefore, that our main hopes for the future must lie.

## NEW BOOKS

*A Textbook of Bacteriology and Immunology.* By JOSEPH M. DOUGHERTY, A.B., M.A., PH.D., and ANTHONY J. LAMBERTI, B.S., M.S. Pp. 360, with 102 illustrations and 10 tables. London: Henry Kimpton. 1946. Price 22s. 6d. net.

This book is apparently intended primarily for nurses in training and for students as preliminary reading prior to taking a university course in bacteriology. It gives a useful history of bacteriology and covers in a superficial manner the general properties of bacteria and their relation to disease. The bacteriology of water, milk and food is discussed and there are chapters on the viruses and parasitic protozoa. The subject of immunity is dealt with more thoroughly than is usual in books of this type, and there is a good deal of technical detail, such as recipes for culture media and particulars of serological methods, which would be more appropriate to a larger textbook. The authors have made it one of their main aims to arouse the interest and enthusiasm of the beginner in bacteriology and in this they appear to have been largely successful.

*The Centennial of Surgical Anæsthesia:* an annotated catalogue of books and pamphlets exhibited at the Yale Medical Library in October 1946, computed by JOHN F. FULTON and MADELINE E. STANTON. Pp. 102. New York: Henry Schuman. 1946. Price 4 dollars.

This is much more than a mere catalogue of a book exhibition. It is a carefully documented and annotated bibliography of all the books and pamphlets relating to the early history of surgical anæsthesia.

The first section deals with the earliest methods, from mandragora to mesmerism, and it is interesting to note that the word anæsthesia was employed in 1718 by Johann Quistorp when he wrote his theses "De Anæsthesia," a contribution to the literature which appears to have attracted little notice during the present revival of interest in the history of anæsthetics.

The works of all the well-known pioneers are all carefully listed in their various editions, and the explanatory notes are of great interest. Hickman, Crawford Long, Horace Wells, Jackson, Morton and J. Y. Simpson all have their place in the catalogue, and one can only envy the fortunate visitors who were able to view the actual exhibition of this rich collection of anæsthetic literature. To the medical historian, this book is indispensable and it is certain to be consulted by anæsthetists and others who realise the value of a study of the past.

*W. T. G. Morton's Memoir on a New Use of Sulphuric Ether, 1847.* Yale Medical Library Publication, No. 14. New York: Henry Schuman. 1946. Price 1½ dollars.

Professor John F. Fulton, the distinguished physiologist and medical historian, is to be commended for his decision to reprint the famous letter which Morton addressed to the Academy of Sciences at Paris a hundred years ago. It stands as a dignified statement of his claims to the discovery of surgical anæsthesia in relation to those of Charles T. Jackson and Horace Wells. Jackson suggested to Morton the use of ether locally, as "toothache drops" and mentioned that it produced interesting effects when inhaled; but he did not suspect that it could produce general insensibility to pain. Morton went much further, and reasoned that perhaps when inhaled it might alleviate pain. His experiments on animals were followed by the complete and convincing demonstrations at Massachusetts General Hospital on 16th October 1846. As for the claim of Horace Wells, Morton's partner in dental

practice, his experiments were made with nitrous oxide gas and his public demonstration was a failure, although there is no doubt that he had grasped the principle of inhalation anæsthesia and had passed on the idea to Morton. In his Memoir, Morton gives a full account of his researches and attempts to justify his conduct in taking out a patent for his "Letheon," the name he gave to his coloured ether. "I am the only person in the world," he wrote, "to whom this discovery has been a pecuniary loss." The Memoir, which has not been reprinted in England since it appeared in *Littell's Living Age* in 1848, deserves the attention of the steadily increasing band of students of medical history. It is published by Henry Schuman of New York, and costs 1½ dollars.

*Die Durchleuchtungstechnik der Thoraxorgane.* By E. A. ZIMMER. Pp. 117, with 65 illustrations and one coloured plate. Basel: Benno Schwabe and Co. Verlag. 1946. Price 12 Swiss francs.

In this small book Dr Zimmer describes the technique of screening organs of the thorax. The characteristic pictures of normal lungs and heart are described. A special chapter deals with diseases of the lungs, and typical appearances are well illustrated by diagrams. This is a very useful book for all interested in learning the technique of screening. It contains many useful practical hints not to be found in larger textbooks. While making a plea for the wider use of screening by practitioners, the author does not wish to usurp the function of the X-ray specialist, and he emphasises the limitations of the methods used.

*Practical Chemistry for Medical Students.* By WILLIAM KLYNE. Pp. xvi+460, with 40 figures. Edinburgh: E. & S. Livingstone, Ltd. 1946. Price 20s. net.

This textbook of practical chemistry has developed from the course of instruction given to first-year medical students at Edinburgh University. The author has bravely attempted the impossible in trying to condense into a textbook for a six months' course, a mass of chemical information which it would take the normal student two or three years to absorb.

The ground covered includes sections on chemical apparatus and manipulation, physical chemistry, both theoretical and practical, ionic reactions, inorganic analysis, organic reactions and analysis, and the special study of compounds of biological importance.

The basic facts of medical chemistry are all present, and there is a reasonable amount of detail. The general lay-out of the text is admirable, and the author has obviously spent a considerable amount of time in regimenting the facts into their proper order. The material is extensively cross-indexed, and is remarkably free from error.

It is a book which is calculated not only to give the medical student an excellent start in his scientific training, but also, to act as a reference book for future use. It will probably be more valuable in the latter connection.

*Tuberculosis in the West Indies.* By W. SANTON GILMOUR, M.B. Pp. 221, with two maps and 12 photographs. London: National Association for the Prevention of Tuberculosis.

The investigation made by Dr Gilmour included an extensive survey of Trinidad and Tobago, Barbados, Grenada, St Lucia, the Leeward Islands, British Guiana, and the Bahamas. His report covers economic, dietary, and housing conditions, and contains detailed recommendations for dealing with the problem in each of the areas investigated. The most complete investigation was that of Trinidad, and the figures of tuberculin and mass radiography surveys there are of epidemiological and ethnological interest. While conditions vary slightly from island to island, the Bahamas being worst in this respect the general findings are a high rate of infection and a high incidence of ulcerative lung tuberculosis, mostly of a rapidly



progressive type. Non-pulmonary tuberculosis was seldom seen. We have here the picture of populations still comparatively young in their contact with tuberculosis, living for the most part under poor social and economic conditions, and the facts and recommendations of the report merit careful study.

*Pneumoperitoneum Treatment.* By ANDREW LADISLAUS BANYAI. Pp. 375, with 74 illustrations. London: Henry Kimpton. 1946. Price 33s. net.

Fashions come and go and pneumoperitoneum has attained a vogue in the treatment of lung tuberculosis. A comparative late-comer to this country it has been employed sporadically in several countries during the past half century in the treatment of various medical and surgical conditions, and Dr Banyai writes from a personal experience of twenty-five years of its employment. His book bears the stamp of experience and authority, and he discusses the method from every aspect. The treatment has a wider field of application than in the handling of lung tuberculosis, and its employment in tuberculous peritonitis and in tuberculous bowel ulceration is discussed fully. There are also interesting chapters on its use in the treatment of asthma and emphysema. The book is generously illustrated, and although the quality of the radiographical reproductions is poor in relation to the general standard of the publication they are informative and helpful. Despite a certain amount of repetition the book is good and its publication is timely.

*Laboratory Manual of General Bacteriology.* By L. S. McCLUNG. Pp. 106, illustrated. London: W. B. Saunders Company, Ltd. 1946. Price 6s. 6d.

This loose-leaf manual is designed for use by students taking a practical class in introductory bacteriology. It gives concise instructions for the performance of sixty-one exercises; these have been chosen to demonstrate important facts and principles of general bacteriology, and to give the student practice in common laboratory techniques. The manual also serves as the student's record book, appropriate space being provided for drawings, tabulation of results and comment. Its use should prove a great convenience in the case of classes which have a syllabus similar to that on which the manual is based.

*Essentials of Neuro-Psychiatry.* By DAVID M. OLKON, S.B., A.M., M.D. Pp. 310, with 138 illustrations. London: Henry Kimpton. 1946. Price 22s. 6d. net.

This relatively small book deals with a thorny subject in a manner that is different from many of the larger volumes in so far as the main emphasis is placed on defined facts; that is to say, the terminology is carefully chosen with the declared object of excluding the popular verbiage with which this subject is so commonly presented—a trick of giving new names and descriptions to theories and ideas that deceives no one except the unwary and the superficial thinker. It is a pleasure to read a book which is pruned of frills to the extent of being a reliable guide to the main principles in the evaluation of mental disorder, not necessarily simplified, because nature is never interested in simplicity, rejoicing only in the truth.

Excusing himself in introducing a few chosen criticisms of divergent opinions the author states, with a complete defence, that every presentation benefits and grows by lively discussion and precise information. The chapter devoted to endocrine disorders and mental disturbances occupies only ten pages—too short, no doubt, for the research worker, but packed none the less with a wealth of information, as indeed is the whole work. Perhaps the numerous illustrations occupy relatively too much space, but even so they are mainly very well chosen.

*Psychology of Women.* Vol. I. *Girlhood.* By HELENE DEUTSCH, M.D. Pp. xi+312. London: Research Books Ltd. 1946. Price 21s. net.

This is an interesting and instructive book about a most difficult and complicated topic. The author describes it as a psycho-analytic interpretation but it goes much further than that because it has the rare distinction of being a clear, lucid, clinical

study which can be read easily by anyone with an adequate psychiatric training. It is essentially a humanistic document which shows a wonderful appreciation of the physiological and psychological adjustments which every one has to make to secure reasonable happiness and a sense of security. There is every reason to suppose that the companion volume entitled *Motherhood*, which is promised at an early date, will maintain the high level of the present one. In the meantime this book can be most highly recommended to all interested in the problems concerned with the development of youth.

*The Technical Minutiae of Extended Myomectomy and Ovarian Cystectomy.* By VICTOR BONNEY. Pp. 282, with 242 original drawings. London: Cassell & Co. Ltd. 1946. Price 30s.

This volume is the result of the author's extensive practical experience of conservative gynaecological abdominal surgery. Being an acknowledged master of his subject, this plea for preservation of the uterus and ovaries when these are the seat of benign neoplasms, including endometriosis, and the detailed description of techniques whereby this ideal can be achieved more frequently than is commonly realised, makes this work an important contribution to gynaecological literature. It will do much to stimulate interest and effort, although it is doubtful if many operators will believe conservatism justifiable to the extent of enucleating "two hundred and twenty-five fibroids" or even "forty tumours whose combined weight after removal was 21 lbs."

A chapter is devoted to a consideration of the general principles of the technique of myomectomy. Attention is drawn to the importance of strict antisepsis and hæmostasis, the value of the author's myomectomy clamp, the planning of the primary uterine incision, "tunnelling," enucleation or morcellation of the fibroid, opening the uterine cavity to explore for polypi and finally, reconstruction of the uterus. Thereafter follow eleven chapters describing in detail operations for the removal of fibroids in every possible situation and combination. Each step is described as if the author were demonstrating a case in the operating theatre and every stage is fully illustrated by the author's own unique line drawings. Adenomyomectomy and ovarian cystectomy receive one chapter each, written in the same clear, interesting and readable manner.

Every gynaecologist will find here material to stimulate critical thought and much valuable advice on technical procedures.

*Biology of Tissue Cells.* Essays by ALBERT FISCHER. Translated from the Danish by EINAR CHRISTENSEN. Pp. ix+347, with 26 plates and numerous tables. Copenhagen: Gyldendalske Boghandel Nordisk Forlag. 1946. Price 31s. 6d. net.

This book is a series of essays on the biology of cells as studied in tissue culture under varying conditions. It is impossible in a brief review to do justice to the many interesting facts and theories put forward; only a few of the more basic features can be alluded to.

In tissue culture cells usually appear as primitive units which cannot be differentiated from one another morphologically, nevertheless they do have certain inherent differences which can be made to appear by appropriate means. The author considers that a tissue culture is not merely a mass of independent cell units but behaves as an organised whole and reacts to injury in a co-ordinated fashion, recalling what is seen in repair of tissues in the normal animal.

The types of cell which can be distinguished in simple culture from a fragment of tissue are: the wandering cell or histiocyte, the spindle-cell or fibroblast, and the epithelial cell. The first tends to migrate out rapidly at the margin of the tissue fragment into the culture medium, then comes the spindle cell which tends to form a meshwork, whilst the epithelial cell grows in the form of a sheet or membrane. Epithelial cells from whatever source, e.g. kidney, liver, skin, etc., lose their specific characters and are recognisable merely as undifferentiated epithelial cells. Also

muscle cells, osteoblasts, etc., all appear as spindle cells, or "fibroblasts." This is known as the "histiotypic" form of growth. If, however, the culture is made from complete or partial "organ anlage" differentiation of cells can occur, giving the "organotypic" or controlled form of growth; and with the formation of intercellular substance or the covering by an epithelial sheet the free movement of cells in the medium is inhibited.

To those interested in basic problems of cellular biology this book is a mine of information and makes stimulating reading. The translation is well done; there are a few minor errors in spelling and phrasing which do not detract from the clarity or value of the text. The book is well produced, with a number of photographic plates and many tables and diagrams. There is an extensive bibliography, but it would be an advantage for reference if a much fuller index were provided at the end.

*A Pocket Obstetrics.* By ARTHUR C. H. BELL. Pp. vii+148, with 13 illustrations. London: J. & A. Churchill Ltd. 1946. Price 7s. 6d.

This revision book, written for general practitioners, midwives and students, attempts to present in brief yet readable form the basic facts of modern obstetrics and will be found to be amazingly successful in its object. Obstetrical anatomy, normal pregnancy and labour and the puerperium are covered in twenty-four pages so that the major part is devoted to the problems of pathological parturition. Naturally a previous knowledge of the subject is presumed, and as in the description of the delivery of a breech, "only certain aspects which are of special importance will be mentioned."

Doctors returning to civilian and midwifery practice will not only quickly obtain a bird's-eye view of the subject, but will also be brought up to date by finding reference, which can later be amplified, to recent advances such as the Rh factor, Vitamin K, and chemotherapy. They will also get specific advice for the management of emergency situations.

*Child and Adolescent Life in Health and Disease.* By W. S. CRAIG, B.Sc., M.D., F.R.C.P.E., F.R.S.E. Pp. xvi+667, with 202 illustrations. Edinburgh: E. & S. Livingstone Ltd. 1946. Price 25s. net.

This unique book fills an important gap in medical literature. It is not another treatise on pædiatrics, but a comprehensive account of the evolution of the various public and charitable organisations directed towards the welfare and education of the child in this country from the seventeenth century up to the present time. The first part of the book is devoted to history, and here the author takes us back and vividly reminds us of the appalling conditions under which young children had to live and work in the "good old days." This section is illustrated with a number of old prints which add further interest to the text. The remainder of the book is devoted to a detailed description of the various services in operation at the present time which have as their objective the care and supervision of the child and adolescent in health and disease, and this is followed by a number of practical suggestions regarding future developments in the ever-widening field of child health. Study of Dr Craig's stimulating book will leave the reader in no doubt that, whilst great progress has been made, there is still much to be done now and in the future, if our children are to have their rightful heritage.

## NEW EDITIONS

*An Introduction to Clinical Perimetry.* By H. M. TRAQUAIR, M.D., F.R.C.S.ED.  
Fifth Edition. Pp. 330, with 255 illustrations and 3 coloured plates. London :  
Henry Kimpton. 1946. Price 36s. net.

This magnificent book has reached a fifth edition, which is a measure of its world-wide success and acceptance, a fact that redounds greatly to the credit of the Edinburgh Medical School. The four previous editions have been reviewed in this Journal, and the present one gives the author opportunity for revision and enlargement of which he has taken full advantage, introducing also a foreword by Mr Norman M. Dott, which emphasises the close relationship between the expert in perimetry and the neuro-surgeon at so many angles of their individual work.

It is indeed still the only monograph in the English language which deals adequately with the interpretation and evaluation of pathological alterations of the visual fields as obtained by perimetry and particularly by tangent screen scotometry. The work has become indispensable to the ophthalmologist and neurologist alike and indicates clearly the integration which has grown up between the two. An improved approach to the clinical problem which finds its own reward in the results obtained.

In the hands of the expert perimetry is a fascinating subject, indeed the understanding of the one who takes the field is the all-important factor. This becomes increasingly obvious as one studies Dr Traquair's interpretations and observes how he evaluates his fields in terms of anatomy, physiology, and pathological characteristics of that portion of the visuo-sensory system in which the lesion occurs which produces the pathological field.

Almost fifty pages at the end of the book are devoted to an excellent appendix, a bibliography of 486 references, and author and subject indices, all of which facilitate ready access and the usefulness of this great work to all clinicians. Dr Traquair deserves the most unstinted praise, more especially from his own school.

*Diseases of the Skin.* By GEORGE CLINTON ANDREWS. Third Edition. Pp. vi+937,  
with 971 illustrations. London : W. B. Saunders Company Ltd. 1946. Price  
50s. net.

In the preface the author states that every page has been rewritten and almost every paragraph revised ; new diseases have been added and the new forms of treatment described. Eruptions due to the newer drugs are also described. No mention is made in the section on Acne Conglobata of the skin bridges, one of the most notable and characteristic features of the disease, and it is surprising to find no description of the thallium acetate treatment of tinea capitis. The reviewer is interested to find the author so strongly in favour of tuberculin injections in the treatment of lupus vulgaris. Helpful details are given of X-ray dosage in the treatment of various diseases, but more detailed instructions in the use of other remedies would be welcome. The book is copiously illustrated with excellent photographs and can be thoroughly recommended.

*Buchanan's Manual of Anatomy.* Seventh Edition. Edited by F. WOOD JONES,  
D.S.C., M.S.C., M.B., B.S., F.R.S., F.R.C.S.ENG. Pp. viii+1616, with 48 Plates and  
847 text-illustrations. London : Baillière, Tindall and Cox. 1946. Price 45s.

The regional basis of this manual, now edited by Professor Wood Jones, assisted by the anatomy staff of Manchester University, has been retained in the seventh edition. The main difference is that histology and most of the general embryology have been

deleted and their place taken by a very useful chapter on the general growth and development of the body as a whole.

The original work was almost entirely illustrated by J. T. Murray, the well-known Edinburgh anatomical artist, and the editor draws particular attention to the fact that many of his beautiful drawings have now been restored. The inclusion of a considerable number of the editor's own diagrammatic figures makes rather an attractive combination.

Another new feature, in emulation of other text-books, is the inclusion of a series of excellent plates illustrating the radiographic anatomy of the body.

The book concludes with a useful glossary of anatomical terms and biographical notes on anatomists whose names occur eponymously in the text. These notes, though not free from error, may serve their purpose of stimulating the student's interest in the history of his subject. The index appears to be full and accurate.

*The Nervous Child.* By H. C. CAMERON, M.A., M.D., F.R.C.P. Fifth Edition. Pp. viii+252, with eight illustrations. London: Oxford Medical Publications. 1946. Price 10s. 6d.

It is not surprising that this well-known book has now reached its fifth edition, since it has always found favour with those interested in the various nervous problems peculiar to childhood. One of the most refreshing aspects of Dr Cameron's book is his simple and straightforward method of approach, and his writing is free from the somewhat confusing terminology which is so apt to find its way into books on nervous and psychological disorders. The author stresses the close relationship between the physical and the nervous in children, a relationship sometimes forgotten by those concerned only with the psychological aspect of a problem. This is a book which should be read by all who have the happiness of the child at heart and who realise that such happiness can only be attained through a proper balance of mental and physical health.

*Complete Denture Prosthesis.* By RUDOLPH O. SCHLOSSER, D.D.S., F.A.C.D., Professor of Prosthetic Dentistry, Northwestern University Dental School. Second Edition. Pp. 466, with 288 illustrations. W. B. Saunders Company, Philadelphia and London. 1946. Price 27s. 6d.

The general arrangement of the new edition of this excellent book does not differ materially from that of the first edition which was published in 1939. Its object is to furnish the student—both undergraduate and graduate—with a guide to a better understanding of the principles involved in complete denture construction. Both clinical and laboratory procedures are fully described but, in compliance with the author's expressed intention to limit the scope of the book, the chemical and physical properties of the various materials used are not described in detail. The text has been brought up to date by the inclusion of the latest advances in technique and in the use of materials employed in impression taking and in the making of denture bases. While the technique described is primarily that taught by the author, various contemporary methods are included which widen the usefulness of the book. The clinical and laboratory procedures are arranged in order of sequence which makes it easier for the student to understand. The book is well illustrated.

*Textbook of Biochemistry.* By BENJAMIN HARROW. Fourth Edition. Pp. xiii+592, with 144 figures. Philadelphia and London. W. B. Saunders Company. 1946. Price 22s. net.

The fourth edition of Harrow's Biochemistry follows less than three years after its predecessor, and indicates the popularity which it enjoys. The general arrangement of the text follows the last edition fairly closely, with numerous additions incorporating recent developments in biochemical research. Many of these additions would benefit from a much more detailed description.

The appendix has also been enlarged to include the details of a number of organic syntheses of biologically important compounds, and it also includes a new section on the elementary properties of solutions. The author covers a very wide field; the subject matter is logically and clearly presented, and the indexing is good.

Although the book is intended primarily for students, and must therefore contain a fair amount of fundamental chemistry, the reviewer feels that the time has come for the omission, from books of this kind, of details which can be found in textbooks of organic and physical chemistry. The saving of space would be considerable, and could be used to expand the more important aspects of Biochemistry proper, and to bridge the gaps between textbooks, reviews, and original papers.

*Management of Fractures, Dislocations and Sprains.* By J. A. KEY and H. EARLE CONWELL. Fourth Edition. Pp. 1322, with 1316 illustrations. London: Henry Kimpton. 1946. Price £3, 3s. net.

In the new edition of this well-known book changes have been made to include methods learned in the war and to incorporate the alterations in treatment brought about by advances in chemo-therapy. The general arrangement is unaltered. The whole range of fractures, dislocations and sprains are adequately covered and after-treatment duly stressed. While alternative methods of treatment are described the authors, as a rule, state the method they prefer.

The chapter dealing with injuries of the spine is outstanding, but the advocated first-aid treatment of fracture-dislocations of the spine in the prone position will not meet with universal acceptance.

The illustrations are numerous; they bring out the various points emphasised in the text and are well produced.

*Aids to Medical Diagnosis.* By G. E. F. SUTTON, M.C., M.D., M.R.C.P. Sixth Edition. Pp. vii+308. London: Baillière, Tindall and Cox. 1946. Price 6s. net.

The whole of this little book has been completely revised so as to bring it abreast of recent advances in medicine. It makes no pretence of being a textbook on medical diagnosis but perusal of any of its chapters will reveal it as something more than a "cram" book.

*American Pocket Medical Dictionary.* Edited by W. A. N. DORLAND, A.M., M.D. Eighteenth Edition. Pp. 1061. London: W. B. Saunders Co. 1946. Price 10s.

This pocket edition of the well-known Dorland has many of the features of the larger work, but the definitions are rather shorter. The selection has been very complete and covers many words of recent origin. A useful little book which can be confidently recommended.

*Clinical Laboratory Diagnosis.* By S. A. LEVINSON, M.S., M.D., PH.D., and R. P. MACFATE, CH.E., M.S., PH.D. Third Edition. Pp. 971, with 207 illustrations. London: Henry Kimpton. 1946. Price 50s. net.

*Clinical Laboratory Diagnosis* contains an account of practically all of the useful laboratory procedures necessary for diagnosis. The book includes sections dealing with immunology, bacteriology, skin tests, pædiatrics, milk and water analysis, and forensic medicine. In addition, brief notes on anatomy, physiology and biochemistry are included where necessary, and short reviews of outstanding diseases have been added where thought useful.

The third edition includes a section on tropical diseases. Among many new items added are the assay of penicillin in the blood; the diodrast and inulin clearance tests; and the estimation of anthocyanin and phenylpyruvic acid in the urine. New pictures of bone marrow films are also included.

This well printed and beautifully illustrated book should be in the hands of every medical research worker.

# BOOKS RECEIVED

- COOKE, ROBERT A., F.A.C.P. Allergy in Theory and Practice.  
(*W. B. Saunders Company Ltd., London*) 40s. net.
- DANIELS, LUCILLE, M.A., WILLIAMS, MARIAN, M.A., WORTHINGHAM, CATHERINE, M.A. Muscle Testing. Techniques of Manual Examination.  
(*W. B. Saunders Company Ltd., London*) 12s. 6d. net.
- ELLIS, RICHARD W. B., F.R.C.P. Child Health and Development.  
(*J. & A. Churchill Ltd., London*) 18s.
- Edited by ELLIS, RICHARD W. B., O.B.E., M.D., F.R.C.P. Child Health and Development  
(*J. & A. Churchill Ltd., London*) 18s.
- FIELD, E. J., M.D., M.S., and HARRISON, R. J., M.A., M.B., B.CHIR. Anatomical Terms. Their Origin and Derivation.  
(*W. Heffer & Sons Ltd., Cambridge*) 7s. 6d. net.
- GIBBERD, G. F., M.B., M.S.(LOND.), F.R.C.S.(ENG.), F.R.C.O.G. A Short Text-book of Midwifery. Fourth Edition  
(*J. & A. Churchill Ltd., London*) 21s.
- GRANIT, RAGNAR, M.D. Sensory Mechanisms of the Retina.  
(*Oxford University Press, London*) 35s. net.
- GROLLMAN, ARTHUR, F.A.C.P., and SLAUGHTER, DONALD, B.S., M.D. Cushny's Pharmacology and Therapeutics. Thirteenth Edition.  
(*J. & A. Churchill Ltd., London*) 45s.
- HAMILTON-PATERSON, J. L., M.D., Second Edition.  
(*Staples Press Ltd., London*) 5s. net.
- HARRISON, G. A., B.A., M.D., etc. Chemical Methods in Clinical Medicine. Third Edition  
(*J. & A. Churchill Ltd., London*) £2
- HAWK, PHILIP B., PH.D., OSER, BERNARD L., PH.D., and SUMMERSON, WILLIAM H., PH.D. Practical Physiological Chemistry. Twelfth Edition.  
(*J. & A. Churchill Ltd., London*) 50s.
- HUMAN, J. U., M.R.C.S., L.R.C.P., L.D.S., D.A. Blind Intubation and the Signs of Anaesthesia. Third Edition  
(*H. K. Lewis & Co. Ltd., London*) 10s. net.
- HYMAN, HAROLD THOMAS, M.D. An Integrated Practice of Medicine. In 4 volumes, with separate Diagnosis and Subject Index. 4336 pages, 6" x 9", with 1184 Illustrations and 319 Tables of Differential Diagnosis.  
(*W. B. Saunders Company Ltd., Philadelphia and London*) £12, 10s.
- JOSLIN, ELLIOT P., SC.D., ROOT, HOWARD F., M.D., WHITE, PRISCILLA, M.D., MARBLE, ALEXANDER, M.D., BAILEY, C. CABELL, M.D. The Treatment of Diabetes Mellitus. Eighth Edition  
(*Henry Kimpton, London*) 50s. net.
- LEE, DE B. JOSEPH, M.D., and GREENHILL, J. P., M.D. Principles and Practice of Obstetrics. Ninth Edition  
(*W. B. Saunders Company Ltd., London*) 50s. net.
- MOBLEY, H. E., M.D., F.A.C.S. Synopsis of Operative Surgery. Second Edition  
(*Henry Kimpton, London*) 30s. net.
- Edited by MONCRIEFF, ALAN, M.D., F.R.C.P. A Textbook on the Nursing and Diseases of Sick Children. Fourth Edition.  
(*H. K. Lewis & Co. Ltd., London*) 30s. net.
- OLSON, Lyla M., R.N. Improvised Equipment. Fourth Edition.  
(*W. B. Saunders Company Ltd., London*) 7s. 6d.
- PATERSON-HAMILTON, J. L., M.D. Penicillin in General Practice. Second Edition  
(*Staples Press Ltd., London*) 5s. net.
- RANSON, STEPHEN WALTER, M.D., PH.D. Revised by Sam Lillard Clark, M.D., PH.D. The Anatomy of the Nervous System. Eighth Edition.  
(*W. B. Saunders Company Ltd., London*) 32s. 6d.
- READ, GRANTLY DICK, M.A., M.D. The Birth of a Child.  
(*William Heinemann, London*) 5s. net.
- RUBIN, I. C., M.D., F.A.C.S. Uterotubal Insufflation.  
(*Henry Kimpton, London*) 50s. net.
- SAINT, CHARLES F. M., O.B.E., M.D., M.S., F.R.C.S.(ENG.), F.R.A.C.S.(HON.). Surgical Note Taking. Fourth Edition.  
(*H. K. Lewis & Co. Ltd., London*) 4s. 6d. net.
- SIMPSON, KEITH, M.D. Forensic Medicine  
(*Edward Arnold & Co., London*) 16s. net.
- SPIES, TOM D., M.D. Experiences with Folic Acid.  
(*The Year Book Publishers, U.S.A.*) \$3.75
- TREVES, Sir FREDERICK, BART., G.C.V.O., C.B., LL.D., F.R.C.S. Revised by CECIL P. G. WAKELEY, C.B., D.SC., F.R.C.S., F.R.S.E., F.A.C.S.(HON.), F.R.A.C.S. Eighth Edition  
(*Cassell & Co. Ltd., London*) 15s. net.
- WELSH, FAUSET, F.R.C.S.(ENG.). Elements of Surgery.  
(*Oxford University Press, London*) 7s. 6d. net.

# Edinburgh Medical Journal

*April and May 1947*

## THE ACTION OF SALICYLATES IN RHEUMATIC FEVER

By A. J. GLAZEBROOK and BRIAN COOKSON

*From the Clinical Laboratories of the Royal Infirmary, Edinburgh*

THE value of a decoction of willow bark as a remedy for painful joints has been recognised by the Hottentots for hundreds of years, the secret being passed down from generation to generation of tribal doctors. It was not until 1874, however, that Maclagan (1881) ascribed a specific action to salicin in the treatment of acute rheumatism, and introduced the remedy into Scotland. About that time, a cheap method of manufacturing sodium salicylate was discovered, and this drug came into general use as an anti-rheumatic; being replaced to some extent by acetyl salicylic acid when the latter compound was prepared commercially in 1889.

It is instructive to read, in Maclagan's own words, of the reasons which caused him to introduce a method of treatment new and untried in Western civilisation; and to reflect how little we have advanced since his day in our understanding of the mode of action of the salicyl radical.

"In connection with the action of quinine on the various forms of intermittent fever and remittent fever, one fact had strongly impressed me—that the maladies on whose course they exercise the most beneficial action are most prevalent in those countries in which the Cinchonaceæ grow most readily—nature seeming to produce the remedy under climatic conditions similar to those which give rise to the disease. Impressed with this fact, and believing in the miasmatic origin of rheumatism, it seemed to me that a remedy for that disease was most hopefully to be looked for among those plants and trees whose favourite habitat presented conditions analogous to those under which the rheumatic miasma seemed most to prevail. A low-lying, damp locality, with a cold rather than a warm climate, are the conditions under which rheumatism is most likely to prevail."

Thus Maclagan was led unerringly to use a principle, salicin, derived from willow bark; and a short experience of it sufficed to show that his expectations were likely to be more than realised.

While salicin was hailed as a cure in Maclagan's time, he recognised that complications, such as carditis, were not likely to be benefited by it, and most of us to-day would agree that no permanent effect upon



the disease process is exerted by the drug. One of us (A. J. G.), by the kind permission of Dr John Eason, has followed a number of cases of rheumatic fever treated with anti-streptococcal serum in the Edinburgh Royal Infirmary; together with other cases of rheumatic fever treated with streptococcal and rheumatic human convalescent serum, for a period of at least five years after the acute attack. The series totalled 103 cases altogether; salicylates were entirely withheld during the acute phases of the illnesses; the incidence of permanent cardiac damage amounted to 56 per cent. This incidence of carditis is certainly no greater than that reported in comparable groups.

### RECENT WORK WITH SALICYLATES

Coburn and his colleagues (1943) claimed that a plasma salicylate concentration of 36 mg. per 100 ml., maintained while the sedimentation rate was increased, prevented carditis. Ten g. to 13.3 g. of sodium salicylate, with an equal quantity of sodium bicarbonate, is the daily adult dose necessary to reach such a plasma concentration and such therapy stops symptoms in one to two days. According to Coburn, plasma concentrations of less than 20 mg. per 100 ml. relieve symptoms but mask active heart inflammation, and he advocates intravenous administration in order to secure a rapid build-up of the plasma salicylate level.

Keith and Ross (1945) were unable to confirm Coburn's claims that massive doses of salicylates prevented carditis; neither did they find that the blood sedimentation rate returned to normal any more quickly under his regime. They realised, however, that the number of cases treated was too small for any unequivocal conclusions to be reached. It must be noted also that, although they used Coburn's dosage, the plasma levels they achieved in their patients ranged from 27 mg. to 31 mg. per 100 ml.; less than that advocated by Coburn. Taran and Jacobs (1945) were also unable to substantiate fully Coburn's work as regards carditis, but they are in full agreement that significant results are obtained by doses of salicylates large enough to maintain a plasma concentration of from 35 mg. to 45 mg. per 100 ml., and they recommend a dosage of 1.5 g. of sodium salicylate per lb. body weight per day. Manchester (1946) considers that a minimum blood level of 25 mg. per 100 ml. is necessary to suppress rheumatic infection in young adults; such a level is exceeded by a satisfactory margin with 10 g. to 12 g. of sodium salicylate per day.

### TOXIC EFFECTS OF ORAL AND INTRAVENOUS SALICYLATES

Coombs, Warren and Higley (1945) were impressed by the toxicity of plasma salicylate levels of over 30 mg. per 100 ml. obtained by the intravenous or oral administration of from 10 g. to 16 g. sodium salicylate daily. They emphasised the occurrence of hyperpnoea, pustular acne and maniacal delirium. Fashena and Walker (1944)

consider that a plasma concentration of 35 mg. per 100 ml. is on the toxic border line for children.

On the other hand, Taran and Jacobs, at a dosage of 1.5 g. per lb. body weight per day by mouth, together with an equal quantity of sodium bicarbonate, noticed tachypnoea in only one out of eighteen children, and none of the others showed any untoward symptoms or evidence of salicylism. Manchester ignores in his account mild toxic reactions such as nausea, vomiting, deafness, tinnitus, vertigo and sweating; he found that 17 per cent. of his cases given 10 g. of salicylate per day developed severe symptoms consisting of tachypnoea in 3 per cent., and severe dyspnoea in 14 per cent.; this latter manifestation could be prevented by adding 0.8 to 1.0 g. sodium bicarbonate to each gram of salicylate. Keith and Ross found, using Coburn's dosage, that symptoms such as epigastric distress, nausea, vomiting, tinnitus and deafness were common for the first few days only of treatment, afterwards most of their patients tolerated the drug well and it was only necessary to stop administration because of severe symptoms of hyperpnoea, acne or of semi-coma in three out of 121 cases. Fletcher (1946) noticed the following toxic effects at plasma concentrations exceeding 30 mg. salicylate per 100 ml.: epigastric distress in 92 per cent. of the cases, nausea in 85 per cent., vomiting in 55 per cent., tinnitus in 92 per cent., deafness in 86 per cent., vertigo in 77 per cent., and headache in 39 per cent. These were present during the first week of treatment, tending to wear off as the patients became accustomed to the drug. Less common manifestations were hyperpnoea in 8 per cent., being so severe in two cases that salicylates had to be discontinued; albuminuria, of slight extent and disappearing soon after cessation of the drug, in 6 per cent.; excessive diaphoresis in 3 per cent.; mental confusion in 1 per cent.; depression of hæmoglobin and of red cell count in 2 per cent.; and hæmorrhagic tendencies in 3 per cent. Two of the three cases who developed bleeding tendencies were already suffering from a blood dyscrasia. The dosage of salicylate producing these symptoms ranged from 6 g. to 10 g. daily, given orally without bicarbonate.

While physicians vary somewhat in their views regarding the toxic effects of large doses of orally administered salicylates, opinions seem to be hardening against the intravenous method of treatment. Taran and Jacobs in nine children given 1.5 g. per lb. body weight per day of sodium salicylate intravenously, noticed salicylism in eight, and two of these children subsequently developed alarming tachypnoea and died. Manchester found that 17 per cent. of adult patients became delirious when given 10 g. of sodium salicylate intravenously per day. In addition, another 6 per cent. had tachypnoea, 3 per cent. severe dyspnoea, 3 per cent. excessive vomiting, 3 per cent. renal pain, and 3 per cent. skin eruptions. Fletcher has shown that intravenous methods of administration offer no advantages over oral methods from the point of view of obtaining high plasma concentrations, as

quicker absorption by the intravenous route was more than offset by quicker excretion. Manchester, Taran and Jacobs also agree that effective blood levels are easily obtained by oral medication. It would seem that the technical difficulties, the annoying symptoms and the possible hazards of intravenous therapy are not counterbalanced by any real advantage over oral therapy.

### RÔLE OF SODIUM BICARBONATE

Sodium bicarbonate is customarily prescribed with salicylate in order to counteract gastritis and renal damage, and to offset acidosis. Fletcher did not find bicarbonate of any value in combating epigastric discomfort, nausea or vomiting; he even noticed that bicarbonate caused exacerbation of epigastric discomfort in some. Not one of his cases suffered severe renal damage, in spite of the absence of bicarbonate, although 6 per cent. had slight temporary albuminuria. He does not comment, however, upon the effect of bicarbonate in the 8 per cent. of his subjects who developed hyperpnœa.

As regards alterations in the acid-base balance, the evidence is confusing. Johnson (1930) and Fashena and Walker (1944) attribute the decreased alkali reserve they found after exhibition of salicylate to a fixed base acidosis. Manchester found that the administration of bicarbonate with salicylate in equal amounts definitely prevented a fall in alkali reserve which occurred when salicylates were given alone, and he also found that the bicarbonate prevented dyspnœa, which he therefore assumed was related to this fall in alkali reserve. On the other hand the results of many other workers go to show that the salicyl radical has a specific action in stimulating the respiratory centre, and that the resulting washing-out of carbon dioxide from the blood causes an alkaline urine to be excreted, with a secondary loss of fixed alkali (Veil and Graubner, 1926; Odin, 1932; Bowen, Roufa and Clinger, 1936; Dodd *et al.*, 1937; Barnett, Powers, Benward and Hartman, 1942; Guest, Rapaport and Roscoe, 1942; Ryder, Murton and Ferris, 1945).

On the whole, it is quite possible that both accumulation of fixed acids, and a respiratory alkalosis, secondary to hyperpnœa, may contribute in varying degree to blood pH alterations. In addition, the probable influence of liver damage in predisposing towards ketosis must be remembered. As for the mechanism of the action of bicarbonate in alleviating the dyspnœa of salicylism, this is best explained by the observations of Smull, Wegria, and Leland (1944) that bicarbonate has a depressing effect upon the blood salicylate level, and their work has been confirmed by the more recent studies of Manchester (1946), Coombs, Warren and Higley (1945) and Fletcher (1946). Coombs and his colleagues showed that blood salicylate depression occurred because bicarbonate increased the excretion of salicylate; and Fletcher further found that this diuretic action of

bicarbonate could be prevented by restriction of fluid intake. It seems that a daily dose of 8 g. sodium salicylate will achieve a plasma concentration of 36 mg. per 100 ml. of salicylate in the average adult ; but that if an equal dosage of bicarbonate be given with the salicylate, then the daily dose of salicylate must be increased to 12 g. to obtain the same plasma concentration.

Thus it is easy to see that bicarbonate may relieve salicylate dyspnoea, whether this be due to a fixed base acidosis or a specific stimulation of the respiratory centre by the salicyl radical ; simply by increasing the excretion of salicylate and lowering the blood salicylate concentration. It does not seem altogether desirable, however, to give alkali to a patient suffering from a respiratory alkalosis ; unless the patient had severe tachypnoea, omission of the next dose of the rapidly excreted salicylate would perhaps be the more rational procedure. Furthermore, it is not wise to give larger quantities of salicylate than are essential ; the full actions of this drug upon the metabolic processes are not yet understood, yet, in giving bicarbonate as well, we are forced to use a bigger dose of salicylate than would otherwise be necessary. The evidence suggests that salicylates should be administered alone in the first place, without bicarbonate, in order to build up an optimal blood concentration as quickly as possible ; bicarbonate can be given later if symptoms of salicylism become urgently severe.

#### PARA-AMINOBENZOIC ACID AND SALICYLATES

While bicarbonate depresses the blood salicylate level, the work of Dry, Butt and Scheifley (1946) at the Mayo Clinic, indicated that the concentration of salicylate in the blood obtained by a fixed daily dose of 10.6 g. of sodium salicylate, with an equal quantity of sodium bicarbonate, rose considerably after the supplementary administration of 1.55 g. para-aminobenzoic acid per day. It is not clear whether this phenomenon is dependent on competitive excretion by the kidney, or some other metabolic effect. The finding is interesting, and makes further investigations desirable ; at the moment, its clinical application to the problem of rheumatic fever is obscure.

#### ANTI-COAGULANT ACTION OF SALICYLATES

Fresh light was thrown upon salicylate action when Link and his colleagues (1943) observed that dicoumarin undergoes some breakdown in the body before it affects the blood prothrombin level. Further work seemed to show that only compounds which could theoretically break down into salicylic acid or orthohydrobenzoic acid on degradation were anti-coagulants ; and this led to the discovery that a single dose of salicylate induced hypotherbinæmia in vitamin K deficient rats within twelve hours, recovery taking place during the succeeding twenty-four hours.

Since that time some workers have claimed that a fall in the blood prothrombin is caused by salicylates in human beings receiving an adequate dietary (Shapiro, Redish and Campbell, 1943; Meyer and Howard, 1943). Others deny that any change in the blood prothrombin is produced. Coombs, Warren and Higley, for instance, treated 84 cases of rheumatism with from 10 g. to 16 g. of sodium salicylate daily; they did not notice any alteration in the prothrombin index, even when plasma salicylate concentrations exceeding 35 mg. per 100 ml. were maintained.

Besides this sharp difference, it must be remarked that the several who claim an anti-coagulant action of salicylate vary in their estimations of the prothrombin change. Rapaport, Guest and Wing (1943) observed that the prothrombin index fell by 50 per cent. of normal in a series of children receiving from 6 g. to 8 g. of aspirin or of sodium salicylate daily. The children had neither sodium bicarbonate nor ascorbic acid with the salicylate, and Fullerton's modification of Quick's method was used for the determination of the prothrombin time. Fashena and Walker made almost identical observations, but they used Quick's original method for the prothrombin time, with desiccated rabbit's brain instead of Russell viper venom. Fletcher regularly produced a fall of the prothrombin index to only 45 per cent. of normal in both rheumatic and non-rheumatic subjects by the twelve-day administration of 10 g. sodium salicylate daily, given without bicarbonate or ascorbic acid. He noticed that the depression became evident at an earlier stage the higher the dosage, and was more profound with high dosage, taking about six days to return to normal after cessation of 10 g. salicylate per day. Manchester found the mean prothrombin index to fall to between only 80 to 90 per cent. of normal in the subjects receiving 10 g. to 12 g. sodium salicylate per day, over a period of ten weeks, although one case reached 51 per cent. of normal. Manchester does not describe his technique of the estimation of the prothrombin index; Fletcher employed an elaboration of Fullerton's modification of Quick's method, and used ovolecthin in addition to Russell viper venom, to prevent inconsistencies due to hæmolysis, lipæmia, platelets, and speed and duration of centrifugalisation.

#### VITAMINS K AND C AND SALICYLATES

In the early experiments of Link (1941), it was found that vitamin K prevented the anti-coagulant action of salicylates in rats. Nievert (1945) recommends the addition of 10 mg. of vitamin K to every 0.6 g. of acetyl salicylic acid, which he finds neutralises the tendency for the prothrombin index to fall, and prevents post-tonsillectomy hæmorrhage. Shapiro (1944) claims that 1 mg. of vitamin K will usually counteract the effect of 1.0 g. of acetyl salicylic acid in lowering the prothrombin level. Meyer and Howard on the other hand report

that 6 mg. of vitamin K will neither correct nor prevent the hypoprothrombinæmia produced by 5.6 g. of aspirin daily. Clausen and Jager (1946) also deny that vitamin K prevents hypoprothrombinæmia due to salicylates. They claim that the action of salicylates is *via* the liver, and that the utilisation of vitamin K is thus prevented.

There is evidence, however, that ascorbic acid deficiency predisposes to a fall in prothrombin index when either dicoumarin or salicylate is administered, and that this deficiency must be made good before vitamin K can be expected to overcome the resulting prothrombin deficiency (Shapiro, 1944; Richards and Cortell, 1942; Overmann, Stalman and Link, 1942; Fletcher, 1946). Fletcher suggests that there is a relationship between vitamin C and vitamin K in the production of prothrombin by the liver, and that salicylates affect this process by an interference with enzyme systems.

We consider that a feasible hypothesis of the mode of action of salicylates in rheumatic fever could be related to the effects produced by this drug on the coagulating properties of the blood, but, as a preliminary, it seemed important to establish to our own satisfaction that therapeutic doses of salicylates do in fact alter the prothrombin index. The following observations were made upon 12 patients with acute rheumatic fever, and 8 patients who were recovering from chronic non-rheumatic disease, such as hemiplegia, and who were free from infection.

### METHODS

After an estimation of the prothrombin index had been done, each of the 20 subjects was given  $1\frac{1}{2}$  g. sodium salicylate and  $1\frac{1}{2}$  g. sodium bicarbonate per lb. body weight per day, together with 200 mg. ascorbic acid per day. The prothrombin index was thereafter determined at weekly intervals.

Fullerton's modification of Quick's method was used for the prothrombin estimations. Variable results were obtained at first, until the following technique was adopted. The blood was withdrawn in glass syringes sterilised by boiling and afterwards washed out with M/10 sodium oxalate solution, 0.5 c.c. of the oxalate solution being left in the syringe, and blood filled to the 5 c.c. mark, care being taken to release the tourniquet as soon as the needle was in the vein. The mixture was carefully transferred to a tube, bubbles being avoided, and centrifuged for five minutes at 1000 revolutions per minute. The supernatant plasma was pipetted off and stored in a refrigerator until convenient, for a period of from half to two hours.

A water-bath at 38° C. heated a rack of 12 mm. tubes and flasks containing M/40 calcium chloride solution and freshly prepared Russell's viper venom ("Stypven"). One pipette was used to place 0.2 c.c. plasma and 0.2 c.c. Stypven into a 12 mm. tube, and, after an interval of two minutes, 0.2 c.c. of the warm M/40 calcium chloride solution was squirted into the stypven-plasma mixture by means of a

separate pipette, and the stop-watch started. The tube was gently agitated in the water-bath for fourteen seconds, and then withdrawn and held up against a black surface, the agitation being continued. The prothrombin time was taken to be that at which granules of fibrin were first observed, and the mean of three estimations on each specimen of plasma was taken. Controls were always employed, and the control time was found to be fairly constant at from seventeen to eighteen seconds, being sixteen seconds on only two occasions.

### EFFECT OF SALICYLATE ON PROTHROMBIN INDEX

TABLE I  
*Non-rheumatic Subjects ("Normals")*

Week of Therapy.	Prothrombin Index.			Number of Subjects.
	Minimum.	Maximum.	Mean.	
0	94	100	98	8
1	78	94	86	8
2	56	90	69	7
3	70	94	65	7
4	50	78	64	7
5	68	77	70	4
6	60	77	67	4
7	55	77	65	4
8	60	70	65	4

TABLE II  
*Rheumatic Subjects*

Week of Therapy.	Prothrombin Index.			Number of Subjects.
	Minimum.	Maximum.	Mean.	
0	94	108	99	11
1	66	94	79	11
2	56	85	74	10
3	54	80	62	10
4	56	79	61	10
5	54	80	69	8
6	51	80	69	5
7	56	79	64	3
8	52	63	59	3

In one rheumatic patient, no fall in the prothrombin index was observed, and his readings have been omitted from the table. In each of the other 19 subjects, a fall in the prothrombin index was produced and maintained as long as the salicylate administration was continued, and the simultaneous administration of ascorbic acid was unable to prevent this fall.

The results are more in accordance with those of Manchester than with those of Fletcher. It may be that ascorbic acid prevented the

prothrombin from sinking to levels as low as those recorded by other workers. Differences in the technique of estimation of the prothrombin time may also explain the variations in results obtained by different observers.

It should be mentioned here that, while Link's premise regarding the degradation of dicoumarin into salicylate by the body stimulated all other work on this subject, there are reasons for believing that it is not securely founded. The non-appearance of salicylate in the urine after the administration of dicoumarin is one; another is the shorter action of salicylate, as compared with dicoumarin, upon the prothrombin; and a further cogent reason, borne out by our own experiences, is the fact that very large doses of salicylate are required to cause an anti-coagulant effect, which is very much less pronounced than that produced by dicoumarin.

### EFFECT OF VITAMIN K

After a fall in the prothrombin index had been observed, 20 mg. of vitamin K per day was given by mouth to 7 of the non-rheumatic subjects for seven days, the salicylate-bicarbonate-vitamin C medication being maintained, and the prothrombin index estimated again at the end of seven days.

TABLE III

Week of Salicylate Therapy.	Prothrombin Index.	
	At commencement of Vitamin K Therapy.	After Seven Days of Vitamin K Therapy.
5	76	88
5	69	66
5	72	100
9	60	100
9	66	104
9	64	96
9	68	86

Thus vitamin K restored the index of 4 out of 7 subjects to normal. It failed to affect the index of one patient, although vitamin C was being given also, and it improved the index of two, although it failed to restore them completely to normal.

### TOXIC MANIFESTATIONS

All 20 patients noticed symptoms, comprising epigastric discomfort, nausea, tinnitus, deafness or vertigo during the first week of therapy. Seven of the patients were sick during the first week. In 18 of the subjects, the symptoms were mild, improved during the second week, and by the third week were of such a minimal nature that they did not really interfere with comfort, although a little deafness and tinnitus tended to persist. No examples of hyperpnœa were



noticed. Albuminuria of slight degree occurred in one of the non-rheumatic cases, and seemed to be related to the administration of salicylates in that one plus of albumen persisted in the urine until treatment was stopped. Hæmaturia or cylindruria was not observed. Changes in the red cell count or hæmoglobin level did not occur in the non-rheumatic patients, and no hæmorrhagic tendencies were seen in any of the patients. Skin eruptions were not seen. Salicylates had to be stopped because of severe toxic reactions in two of the 20 cases, in one because of severe and uncontrollable vomiting, and in another because of the supervention of mental confusion and drowsiness.

The series is too small for much comment to be made upon the effects of the treatment in halting the rheumatic process, but it is worth noting that two of the 12 cases of rheumatic fever developed unequivocal signs of rheumatic carditis while receiving  $1\frac{1}{2}$  g. of sodium salicylate per lb. body weight per day.

### THE MODE OF ACTION OF SALICYLATES

An early explanation was given by Weintraud in 1913, when he suggested that they had a kind of narcotic action upon the specifically irritated tissue cells, similar to the effects of anæsthesia in acute anaphylactic shock.

The antagonism which exists between sulphanilamide and its analogue, para-aminobenzoic acid, is well known; Ivanovics (1942) has drawn attention to a superficially similar antagonism between pantothenate and salicylic acid. He has demonstrated that salicylate in a dilution of M/1000 will prevent the growth of bacteria which synthesise pantothenate, such as the *Staphylococcus aureus* and *B. coli*. The addition of pantothenate to cultures destroys the antibacterial action of salicylate, there being a rough quantitative relation between the two compounds concerned in the reaction. He concludes that salicylate interrupts some vital chain of chemical reaction which eventually leads to the synthesis of pantothenate by staphylococci and *B. coli*. As in the case of para-aminobenzoic acid and salicylate mentioned earlier, it is difficult to see what bearing the relationship between pantothenate and salicylate has upon the problem of rheumatism, although an annotator in the *British Medical Journal* (1945) suggested a clinical trial of salicylate and pantothenate in rheumatic fever, to determine whether the beneficial action of salicylate could be prevented by this accessory food factor.

A more promising line of investigation has been opened by recent work with hyaluronidase. This enzyme is manufactured by many bacteria, and it is of significance to note that they include over 200 strains of hæmolytic streptococci (Kendall, 1937; Duran-Reynals, 1942; McClean, 1941). The principal substrate of connective tissue most affected by rheumatism is hyaluronic acid (Meyer and Palmer, 1936), and this substance is hydrolysed by hyaluronic acid, thus

favouring the spread of liquids, exudates and pathogenic organisms in the mesenchyme. As an example, it has been shown by Guerra (1946) that the "spread" of India ink injected intradermally into rabbits is six times greater when hyaluronidase is added to the ink. Similar results were obtained in human adults and children, using Evans blue intradermally instead of India ink.

More important is the fact that he found intradermal injections of Evans blue and hyaluronidase in individuals with latent or active rheumatic fever gave unique reactions with enormous diffusion of the dye and local œdema. Salicylates have a powerful inhibitory action on the spreading effect of hyaluronidase; in animals, in normal humans, and in rheumatic subjects; the inhibition varying with the dose of salicylate.

Guerra suggests, therefore, that rheumatic fever being a disease of the mesenchyme characterised by the invasiveness rather than the virulence of the causative organism, "spreading" factors such as hyaluronidase are of prime importance, and that the anti-rheumatic action of salicylates is related to their inhibition of this enzyme. The idea is refreshing, for it reveals possibilities of a new conception of the disease.

However, the view that rheumatic fever is an allergic, or, as Levinthal prefers to call it, an anaphylactic phenomenon, is too well established to be further elaborated in this paper. The old theory that an anaphylactotoxin causes harmful symptoms has been abandoned; it is widely held to-day that these are due to the purely physical effects of an intracellular antibody-antigen clash. This postulate is based upon a premise not as yet clearly shown to be fully responsible for the pathological process operative in rheumatism; it demands, however, a fundamental approach to the study of salicylate therapy. On this basis, the therapeutic problem lies in increasing antibody production, so that a sufficient quantity is present in the blood to neutralise circulating antibodies before they reach the tissue cells; palliative measures would aim at upsetting or preventing antibody-antigen reactions, or else at mitigating the harmful effects of intracellular antibody-antigen clashes.

There is no evidence to suggest that salicylates increase antibody production; indeed, the work of Coburn and Kapp (1943) indicates that they have the opposite effect. These American observers mention the findings made by Marrack and Smith (1931) that diphtheria toxin antitoxin floccules are dispersed by salicylates; and the results of Derick, Hitchcock and Swift (1928), who noticed that the serum of patients with serum sickness failed to precipitate horse serum after prophylactic treatment with aspirin.

Coburn and Kapp demonstrated that sodium salicylate prevented the precipitation of antigen by antibody *in vitro*; they thought that this was due to the action of salicylate on antibody. The experiments of Lutwak-Mann (1942) support the view that salicylates have an

action upon the enzymes and metabolic processes of the body. Coburn and Kapp feel, therefore, that salicylates modify the immunity reaction in rheumatic fever by keeping antibody production at a low level, and that this effect is produced by an action upon cellular enzyme systems. This argument is stimulating, but not entirely convincing, for it does not seem logical to expect good results from a treatment which further weakens an already inadequate immunity response.

It may well be that the beneficial results of salicylate therapy are due to the third possibility mentioned, that they alleviate the ill-effects of an antibody-antigen clash occurring within the cell. In considering this question, we have to examine the possible effects of irritation upon the structure of the cell. Heilbrunn (1943) has thought a good deal upon this topic, and he and his colleagues have shown that the sensitivity of protoplasm to many chemical and physical agents is due to the release of calcium, which initiates internal clotting of the cell. Varying degrees of clotting may occur, and incipient cell clotting is reversible. Such clottings, according to Heilbrunn, perhaps play a part in the physiological behaviour of the cell, but complete clotting usually means cell death. The mechanism of cell clotting appears to be similar to that which brings about clotting in the blood, and can be prevented by similar agents, such as, for example, oxalates (Heilbrunn and Daugherty, 1933).

The anti-coagulant properties of salicylates may be of value, therefore, in that they mitigate the physical effects of antibody-antigen combination, which would otherwise cause irritation and various degrees of clotting of the cell protoplasm. If anti-coagulants benefit allergic and anaphylactic states, then heparin should be an agent of prime importance. This substance is most probably secreted under normal circumstances by the mast cells, which have a wide distribution in the body. They are found singly or in clumps; characteristically, they are arranged in close proximity to the walls of small blood vessels, and may even replace the lining endothelium. In acute anaphylactic shock, notably in that of dogs, there is a marked loss of coagulability of the blood, and a similar change, though slighter in degree, characterises the blood of rabbits in anaphylaxis, and of guinea-pigs if the shock is a protracted one.

Quick (1936) came to the conclusion that heparin was the cause of incoagulability of blood in peptone shock, and his ideas were confirmed by Jaques and Waters (1940) who were able to isolate crystalline heparin from the blood of anaphylactic dogs. Further investigations have shown that heparin has marked anti-anaphylactic properties, and that its appearance in the blood during anaphylactic shock cannot be dismissed as an unimportant side-effect. Kyes and Strausser (1926) found that heparin prevented anaphylactic shock in pigeons, and Williams and van de Carr (1927) showed that heparin protected guinea-pigs sensitised with horse serum. Macht, Dunning and Stickel (1928) also described the protective action of heparin

against the shock produced by horse serum in sensitised guinea-pigs, rabbits and rats. Macht (1943) repeating his earlier studies, found that the prior administration of 5 mg. to 10 mg. of 1:80 heparin solution diminished the violence of anaphylactic shock in 25 guinea-pigs, and in some cases prevented the attacks altogether, whereas the majority of his 25 controls had severe reactions and died. He made the interesting observation that ten minutes must elapse before the injection of the antigen to produce an antagonising effect of heparin, and that the simultaneous injection of both heparin and antigen was ineffectual.

If it is true that the anaphylactic state is dependent upon changes in the fluidity of protoplasm brought about by the irritating physical effects of an intracellular antibody-antigen clash, then other agents which cause clotting of blood and protoplasm should bring about a similar clinical picture. Such is indeed the case. Rocha e Silva and Dragstedt (1941) have shown that intravenous injections of trypsin tend to produce extensive intravascular clotting, by a direct action upon the blood. Smaller doses produce effects remarkably similar to anaphylactic shock in corresponding animals, and lead to the liberation of heparin into the blood stream. Rocha e Silva (1939, 1941) also demonstrated that histamine-like substances are released when guinea-pig lungs are transfused with trypsin.

As Heilbrunn points out, cellular clotting brought about by irritation presumably involves the participation of a proteolytic enzyme, and it is easy to see how excitation or excess stimulation of protoplasm might cause the production of histamine from the damaged cells. Ever since the work of Dale and Laidlaw (1919), it has been recognised that histamine, or a histamine-like substance, plays an important part in anaphylactic phenomena, and it seems probable that, if the liberation of this substance from anaphylactically reacting cells could be inhibited, a serious tissue damage might be prevented. Dragstedt, Wells and Rocha e Silva (1941) have stressed that the prominent symptoms of anaphylactic, peptone and trypsin shock are very similar, and they suggest that they are closely related phenomena. They were able to inhibit the release of histamine from cells and plasma, whether this was brought about by peptone shock, trypsin shock, or anaphylactic shock, brought about by a concentration of 0.12 per cent. of heparin in the blood of rabbits. Weaker concentrations, *e.g.* 0.02 per cent. of heparin, failed to inhibit the release of histamine.

Considering the proposition that changes in the viscosity of protoplasm are closely related to anaphylactic and allergic states from a different angle, it is perhaps possible to throw some light upon a mystery that has always intrigued us—the relationship between ascorbic acid nutrition and rheumatic fever. While ascorbic acid is utilised at a greater rate than normal in any infection, this phenomenon is especially marked in rheumatic fever. The rôle of ascorbic acid in hydrogen transport has not been clearly established, but a relationship to

cellular oxidative processes is indicated by the demonstration that ascorbic acid deficiency in guinea-pigs causes a marked drop in succinic dehydrogenase (cytochrome C oxidase) in muscle (Harrer and King, 1941); and in general, it seems not improbable that ascorbic acid plays some part in tissue respiration. There is other evidence that rheumatic fever interferes with enzyme systems. The occurrence of porphyrins in the urine, described by Macmunn in 1880, and later by Kapp and Coburn in 1936, may be cited. Vitamin A levels are much reduced in this disease (Shank *et al.*, 1944; Race, 1937; Ellison and Moore, 1937; Hall *et al.*, 1944), and it has been suggested that unsaturated bonds of vitamin A act as hydrogen acceptors. Glutathione is of fundamental importance in cellular respiration, as it maintains the sulphydryl groups of a great variety of enzymes in a reduced -SH form essential for enzymatic activity. The oxidised moiety of glutathione is greatly reduced in fatal cases of rheumatic fever. On the other hand, there is some evidence that succinate compounds are of value in the treatment of rheumatic fever, even when given without salicylates (Gubner and Szucs, 1945). It is established that succinates and related decarboxylic acids are of importance in biological oxidation (St Gyorgi, 1937; Krebs, 1943; Evans, 1944; Barron, 1943; Green and Colowick, 1944).

Thus there is much to support the contention that rheumatic fever involves, to a serious degree, the enzyme systems of the body, and that ascorbic acid nutrition is concerned as part of a more general enzymatic disturbance. Heilbrunn states that the release of calcium into the cell interior, which follows cellular irritation and precedes viscosity changes, may affect certain types of enzymes; and other investigators (Keilin and Hartree, 1940; Keilin and Harpley, 1941) have shown that the correct functioning of important enzyme systems depends upon the colloidal state of the protoplasm.

The beneficial, but hitherto mysterious, effect of jaundice upon patients with severe chronic rheumatism was first noticed by Still in 1897, but has since been corroborated by several clinicians (Wishart, 1903; Parsons and Harding, 1932; Grigg and Jacobsen, 1933; Sidel and Abrams, 1934; Borman, 1936; Hench, 1938; MacCallum and Bradley, 1944; Gardner, Stewart and McCallum, 1945). The jaundice, in order to influence the rheumatism favourably, must be of an obstructive or toxic (hepato-cellular) type; improvement following hæmolytic jaundice has not, to our knowledge, been described. Hench has studied this problem for some years, and he has found that the concentration of bilirubin in the serum must be at least 8 mg. per 100 c.c. for a remission in joint pain to be brought about; patients may derive quite dramatic benefit if the amount of bile in the blood reaches a high level.

Attempts to demonstrate a direct anti-rheumatic action of bile, or of one of its constituents, have not met with success. Daily intravenous injections both of bile, and of bile salts, have been carried out

in cases of infectious arthritis, but the results have been equivocal (Thompson and Wyatt, 1937; Hench, 1938) although Hench obtained concentrations of bile in the serum approaching 35 mg. per 100 c.c. immediately after injection, and 12.5 mg. per 100 c.c. twenty-four hours later, when the next injection was due. Levinthal (1945) has also failed to show that injected bile affects the antibody-antigen reaction. On the other hand, the production of hepatitis and jaundice by the injection of icterogenic serum has been shown to cause remission in a number of cases of infectious arthritis (MacCallum and Bradley, *loc. cit.*; Gardner, Stewart and McCallum, *loc. cit.*).

Peacock (1938) made the suggestion that jaundice benefited rheumatic joints, not because of the presence of bile in the blood stream, but because of its absence from the intestine. Certainly there is only one obvious common factor which could link the anti-anaphylactic powers of heparin and the anti-rheumatic actions of salicylates and of toxic or of obstructive jaundice, and that is a reduction in the coagulating properties of the blood.

### SUMMARY

Recent work with salicylates is reviewed, and their hypoprothrombinæmic action in both control and in rheumatic subjects is confirmed. The possible significance of hypoprothrombinæmia in mitigating harmful effects of intracellular antibody-antigen reactions, such as release of histamine and disturbances of respiratory enzymes, is discussed. The anti-anaphylactic power of heparin and the anti-rheumatic effects of salicylates and of obstructive or toxic jaundice may be linked by the factor, common to all, of an interference with blood coagulation.

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## THE BASIS OF PROGNOSIS \*

By D. M. LYON, M.D., F.R.C.P.Ed.

THE public expect from a medical man three things: ability to recognise disease, an attempt to restore complete health and some estimate of the future—diagnosis, treatment and prognosis. Of these, diagnosis is clearly the most important since the other two must be based on the decision arrived at. Unfortunately the word "diagnosis" is usually employed in a very restricted sense and implies nothing more than the choosing of an appropriate label. Since the prefix *Διά* may mean through or thorough as well as apart, "a thorough knowledge" is much to be preferred as a definition of diagnosis. The significance is this. In spite of many outstanding advances in medical science in recent years the nomenclature of diseases is far from perfect. Many of the diagnoses we accept and employ are unsatisfactory and quite inadequate, especially as a basis for prognosis. To mention a few, anæmia, diarrhœa and jaundice are mere approximations if used without qualification. Many so-called diseases such as asthma, diabetes, hemiplegia and sciatica should rather be regarded as symptom-complexes since each may depend on various causes. "Pleurisy" and "pyelitis" are inadequate unless the etiological factors are recognised, and even lobar pneumonia can no longer be accepted as a complete and satisfactory diagnosis. The site of the disease may be of importance; anthrax of the lung has a very different significance from a local lesion of the skin, and a cerebral hæmorrhage involving the pons or the ventricles from one that merely presses on the internal capsule. It will be obvious, therefore, that the diagnosis should be as thorough as possible if a really satisfactory prognosis is to be made.

It is interesting to note that, while medical literature contains many books and papers devoted specially to diagnosis and to treatment, the subject of prognosis has received scant attention, though one of the Hippocratic books is devoted to Prognostics.

The word prognosis, like diagnosis, has come to be used in a rather restricted sense. By derivation prognosis means fore-knowledge, and *The New English Dictionary* defines it as "a forecast of the probable course and termination of a case of disease; also the action or art of making such a forecast." Most text-books and even special detailed monographs devote little space to the subject, and sometimes it is omitted altogether. Many writers, under the heading of prognosis, confine their remarks only to the chance of a fatal issue occurring.

\* A Honyman Gillespie lecture delivered in the Royal Infirmary on 30th August 1945.

In point of fact they are really not so remiss as this would seem to indicate, for much of the required information is given under other headings. The ordinary text-book, for example, gives a composite picture of a disease, emphasising the important points and giving a sketch of the usual course. It also mentions modifications which may occur and rarer features that may be encountered. Possible complications and sequelæ are described, and in certain cases figures are quoted to indicate the frequency of these variations. The average picture thus described might be regarded as the normal course of an untreated case. This information is the real basis of prognosis. If all cases of a disease, or even a majority of them, followed a standard course, the framing of a prognosis would be relatively easy, but unfortunately the matter is not so simple. Individual patients suffering from the same disorder may react very differently, and there are many factors which may modify the course of the disease and change its outcome. The causes of such variations are many, and these will demand our attention. Some are of such wide application that they may almost be accepted as general principles, while others are much more restricted and apply to one or only to a few disorders.

The search for general principles in the art of prognosis is made difficult by the very diverse nature of disease. Consider how very different are the problems presented by diseases from scabies to anthrax, or from ingrowing toe-nail to fracture of the spine. Some diseases remain strictly local, others show general effects, or there may be a constitutional disturbance with no apparent local lesion. The variety in type and course is very great.

Prognosis may refer to various stages of a disorder, the acute or active phase, the convalescence, and the after-life. It has been divided into prognosis *quoad vitam* and prognosis *quoad restitutionem ad integram*; into immediate and remote. In the early stages, the question of the probable length of the acute phase may arise, the chance of survival or death, the possibility of complications and so forth. Looking further ahead, there is the question of possible residual incapacity—its degree and duration, the chance of recurrence or reactivation, the liability to other disorders, and whether the disease will have any effect on the expectation of life.

### IMPORTANCE OF THE PROGNOSIS

To the patient and his friends the prognosis may seem to be of much more importance than the diagnosis. He will want to know how long the illness is likely to last; what will be the outcome? Will he survive or die? How soon will he be out of danger? How long will he require to convalesce? When will he be fit to return to work? Will any disablement or incapacity remain? Can he look forward to normal activity without any impairment of the expectation of life?

Such questions should not be regarded as due to idle curiosity. The answers are often of extreme importance. Arrangements may have to be made for carrying on the patient's work during his period of incapacity. The relatives will want to know how much nursing attention will be required in order to decide whether they can cope with the demands, or whether special arrangements must be made for assistance or for getting the patient transferred to an institution for treatment. If the condition is serious and there is a possibility of a fatal issue, members of the family may have to be summoned or the lawyer may have to be called in to settle the patient's affairs. The patient may have to be warned of possible risks (sudden death in a patient recovering from coronary infarction), or of the likelihood of recurrence (cardiac failure).

Prognosis, in its wider sense, has also an importance for the doctor himself. His knowledge of the future trend of the disease will allow him to anticipate and perhaps avoid certain dangers. Thus prognosis may determine his line of treatment, and may in an extreme case save the life of the patient. A timely warning of possible danger may safeguard the doctor's own reputation as an able practitioner.

Life insurance is founded on a basis of prognosis. Individuals apparently healthy are accepted at standard rates, but many impairments require to be considered in the light of their possible effect on the expectation of life. Special terms are usually required for such things as a family history of tuberculosis or insanity, a personal history of peptic ulcer, exophthalmic goitre or rheumatic fever, the presence of scoliosis, hernia, otosclerosis, obesity or a raised blood pressure.

What is the real position of prognosis? In recent years great advances have been made in the diagnosis and the treatment of disease, but the same cannot be said of prognosis.

A good deal is already known about prognosis in a general way, but there is little exact information on the subject, and it can hardly be said to have attained the dignity of a science. The general principles which should guide in forecasting the outcome of a disease are fairly well understood, but there is a great lack of exact data which should be available.

Large numbers of case records should be accumulated and analysed so that the figures might be available for such things as the duration of the illness, the frequency of complications, the chance of complete recovery or of impairment of health, and the effect on the expectation of life. Only in this way is advance possible. Even when exact information has been recorded and a complete picture of the average case has been obtained, prognosis in the individual patient will remain a difficult task because so many variables have to be taken into account, and the best-trained physician will still have to rely very largely on his own experience and common sense.

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Fig. 1

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1938/39/40. Treatment as out-patient continued throughout this period with applications of Cod Liver Oil and Ichthopaste beneath Elastoplast bandages. Area of ulcer constantly diminished.

January 1941. Hard scar was removed from base of ulcer which was lightly packed with Jelonet, covered with Ichthopaste and bandaged tightly with Elastocrepe.

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Fig. 2

*Roentogram showing site  
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## THE FACTORS WHICH INFLUENCE PROGNOSIS

The factors which must be considered in drawing up a prognosis for any individual case may best be arranged under the headings: the patient; the disease, its cause and the reaction to it; the doctor and his treatment.

*The Patient.*—As different kinds of soil may influence the growth of a plant, so circumstances peculiar to the individual may modify the effect of a disease agent. In many cases the *condition* of the patient before the onset of the illness will play a profound part in determining the type, severity and course of the disease, and is therefore of great importance in forming a prognosis. Account should be taken not only of his physical and mental state immediately before the disease appeared, but of his earlier medical history or even of his ancestry, for all that has gone before has contributed to his make-up, and some of the factors may determine the course of the illness.

The exact influence of *race* and *heredity* on health and disease is always difficult to determine, because it is usually impossible to set aside the effects of environment and habit. As examples of the importance of race, pneumonia and tuberculosis are more serious amongst negroes, while scarlet fever is said to be less formidable in Mediterranean peoples.

The *family history* may be illuminating. Longevity often seems to be an inherited trait, and there are good stocks which satisfactorily resist disease and tend to attain old age. Other families may show a poor resistance to infections or a tendency to succumb to cardiovascular troubles at an early age. Knowledge of any special tendency amongst the patient's relatives may be of help when the prognosis is being considered. A marked family history of diabetes is considered unfavourable, and the outlook for a chronic alcoholic is less good if there have been other cases in the family.

The previous *medical history* of the individual may be important in several ways. An earlier disease may have weakened the constitution and resisting power or may predispose the patient to certain complications. A history of syphilis aggravates the prognosis in angina pectoris or in aortic incompetence. An old otitis media may light up during the course of an acute infection in some other part of the body. In some cases the fact that there has been a previous attack of the same trouble demands a more serious prognosis. Each recurrence of rheumatic fever increases the gravity of the outlook and renders cardiac involvement more likely. The prognosis is less favourable in repeated attacks of delirium tremens. Recurrent attacks of bronchitis or nephritis tend to cause more permanent damage and so warrant a less favourable prognosis.

The *co-existence of some other disease*—often of a chronic or general nature—may profoundly influence the power of recovery and

so demand a less hopeful prognosis. Chronic diseases of the heart, lungs or kidneys are important in this connection. Chronic nephritis and arteriosclerosis reduce the chance of recovery in acute diseases. Diabetics react badly to pneumonia and other acute infections and tuberculosis is a particularly serious complication in these cases.

Similarly the existence of a chronic focus of infection may delay recovery. Glycosuria in diabetes may persist until some focus, often quite a small one such as a root abscess, has been discovered and eliminated. An attack of bronchitis may be prolonged by the presence of an unsuspected bronchiectasis.

The *constitution* or general make-up of the patient has often an important influence on his reaction to disease. A well developed physique in first-class condition is usually considered an asset. Certainly a person in good bodily health should be able to resist an infection or a wasting disease which would tax a weaker individual to the limit. A subject who has previously been in the best of health will be able to withstand a severe and prolonged illness better than one who is already in poor physical condition. Though this be true in general, exceptions sometimes occur. It is well known that, in such epidemics as influenza and cerebrospinal fever, the apparently robust may have no better chance than less favoured individuals. Previous vigorous health does not appear to offer any advantage in such conditions as angina pectoris and cerebral hæmorrhage.

Another point of some importance is that the less robust individual may often give in to the illness, seek assistance and take to bed at an earlier stage, whereas the person unaccustomed to sickness may do harm by trying to fight against his complaint.

The state of *nutrition* may have a profound influence on prognosis. Obesity is always a disadvantage, and it is well known that excess weight is associated with a lessened expectation of life. The obese do not withstand acute infections well, and excess weight is a distinct disadvantage in diseases of the heart and respiratory system. On the other hand, malnutrition, anæmia and emaciation are also of importance, and such debilitating influences as overwork, exhaustion and sleeplessness may profoundly affect the outlook. Thin and undernourished individuals as a rule react poorly to acute infections and their time of recovery is often unduly prolonged. In such persons the disease may assume a more serious type and complications may be more apt to occur.

A good sound constitution with the vital organs in a healthy state should warrant a better outlook than one where any of these is defective.

Account must be taken of certain *habits*. Addiction to alcohol, tobacco or drugs may definitely impair prognosis. The alcoholic reacts badly to acute infections in general and has a very high mortality rate in lobar pneumonia. He is not reliable, his judgment is impaired, and he may take risks which another person would avoid. The effect

of excessive indulgence in tobacco is less easily assessed. Continued smoking is said to delay healing in peptic ulcer, and it is usual to forbid smoking altogether in certain diseases of the heart. The question is not a simple one, since excessive use of tobacco may be an expression of a neurosis, and the soothing effect of smoking may have to be taken into account.

Over-indulgence in the pleasures of the table is believed to be a cause of disease, but its effect on prognosis is not very obvious, though over-eating may offer embarrassment in cases of valvular diseases of the heart.

Lack of sufficient exercise may be of some importance. A sluggish, idle individual with flabby muscles may have a poorer chance of recovery than one who has been reasonably active and has kept himself physically fit.

*Economic Status.*—As Saundby so aptly said, "a competent income and a tranquil existence count for much in prognosis" of most chronic diseases. Practitioners whose work takes them amongst patients of all social grades are constantly struck by the fact that poverty may handicap recovery which an adequate competence would allow. Under-nourishment and poor hygienic surroundings may have undermined the constitution and impaired the resistance. During an illness adequate feeding and efficient nursing care may make all the difference; but the economic factor does not end here for, after the acute phase is over, poverty may continue to exert a baneful influence on the patient's future. The labourer with chronic bronchitis, who has to support his family by outdoor work, will have a poorer prognosis than the bronchitic who can afford to take proper care of himself. The housewife who has mitral stenosis will risk a further breakdown if, without domestic assistance, she has to look after a family. The prognosis in such conditions as angina pectoris and chronic nephritis is vastly better in those who can afford to live within their restricted capacity and take care of themselves.

While the disadvantages of a poor economic status are obvious, it must be remembered that certain infections may hit the well-to-do as heavily as the poor. The coddled, over-protected and pampered child may face disease with a handicap, and even rickets is not unknown in luxurious surroundings.

*Occupation.*—Quite apart from its effect on the economy of the home, the occupation of the patient may have an important effect on prognosis. Alcoholism is more difficult to control in those who are associated with "the trade," as are other forms of addiction in those who have legitimate access to the drug. Closely related and sometimes not to be separated is the effect of *environment*. The alcoholic who cannot avoid lively company has a poor chance of recovery. Recurrent asthma may depend very largely on environmental factors, and the outlook in anxiety neurosis may depend on whether the environment can be controlled or changed.



*Sex.*—Though often of great importance in the incidence of certain diseases, sex has little effect on prognosis. Minor differences have been recorded in the sex mortality of some diseases; for example, females are slightly less liable to die from pneumonia, but on the whole the differences are not great. Women as a rule submit to therapeutic restrictions more readily than men, and are not so apt to take risks which may involve future trouble. Endocarditis is said to be more common in females after an attack of rheumatic fever.

*Pregnancy*, however, is of importance to prognosis in many pathological conditions. Scarlet fever is a particular risk in pregnancy and the puerperium; and pregnancy aggravates the prognosis in diabetes.

*Age.*—The age of the patient has an extremely important bearing on prognosis in many conditions. In general, the recovery process is very active in the growing child; small clean wounds in the young will heal with a rapidity which surprises their elders. Age is one of the most weighty factors in determining the outcome in pneumonia; mortality during adolescence is practically nil, but with each successive decade it rises to reach a high level in old age. A similar state of affairs is seen in cerebrospinal meningitis. Diabetes in the young is usually acute and serious, and is still grave in those under the age of forty; on the other hand, when the disease begins in later years it usually runs a milder course.

Infants and young children react powerfully; they are easily upset by acute illnesses and sometimes their hold on life seems very precarious. Scarlet fever is most fatal in early years and the mortality declines after puberty.

*Mental Status of the Patient.*—Mind has great influence over bodily functions, and the temperament of a patient may play a great part in his recovery. In general, an optimistic, cheery outlook and an easy mind free from anxiety or worry will favour recovery. Depressing emotions and apathy may have an adverse effect. Sometimes the degree of *intelligence* is of importance. In diabetes, for example, the patient must be able to understand the rules laid down for him, and he must also be able to appreciate when danger threatens and when help should be sought. Real stupidity in medical matters is sometimes found in persons of otherwise high mental attainment. *Will power* may also be an asset. In the treatment of obesity by dieting, for example, ability to persevere is absolutely necessary if a satisfactory result is to be attained. In both of these diseases the will to co-operate and the desire to be fit may make all the difference between success and failure.

Lastly there is the element called *pluck* which sustains the person gravely ill, and the *will to live* which may preserve the patient whose case seems hopeless. The mental factor in disease is one which certainly deserves more attention than it has hitherto received.

## THE CAUSE OF THE DISEASE—THE AGENT

(a) *Bacterial Disorders*.—Many disorders with which we have to deal are of microbial origin, but it must be clearly understood that the mere presence of a pathological organism in the body does not constitute disease, nor does it always cause an illness. Persons may harbour the pneumococcus without ill effect; diphtheria or typhoid carriers may themselves show no evidence of disease. Why it is that trouble should occur at some times and not at others is not altogether clear. In some cases the "resistance" of the patient may prevent disease, while in others the explanation may lie in the organism itself. It is now known that certain organisms are really groups, individual members of which possess different pathogenic capacity. Certain of the thirty-odd types of pneumococci are relatively harmless, while type III causes a much higher mortality than the other common types, I and II.

Apparent variations in the course of a disease may be due to an incomplete knowledge of the causal agent, for similar disease reactions may often be produced by different organisms. Lobar pneumonia, for example, may be due not only to a pneumococcus but also to streptococci, staphylococci, *B. Friedlander*, viruses, etc., and naturally the severity of the lesion and the prognosis may be profoundly affected by the kind of organism present. Acute pyelitis due to *B. Coli* is very easily controlled but is very liable to recur, while coccal infections are often more serious. In either case the presence of some obstructive factor in the urinary tract is likely to delay recovery.

The *mass of infection* or the number of organisms present must be of importance in determining prognosis. A widespread diphtheritic lesion will produce more toxin than a smaller one and will justify a graver forecast. In tetanus it is said that the shorter the latent period the more serious the outlook.

Bacteria may also vary in *virulence*, in their power to harm the body. It must always be difficult for the clinician to distinguish the effects of a heightened virulence from those of a massive infection, either of which will cause a more severe illness and will naturally require a graver prognosis. During an epidemic much help can be obtained by noting the severity of the disease in other patients. It is well known, however, that virulence may change during the course of an epidemic. In pandemic influenza, for example, the early cases tend to be mild, virulence increases to a maximum, then gradually wanes as the epidemic comes to an end. Another well-recognised fact is that lobar pneumonia varies from year to year; sometimes mortality is very low, sometimes it is high and there may be more tendency for complications to occur. In the case of epidemic diseases, therefore, it is well to take account of the general trend of the current infection before forming an individual prognosis.

Statistically it has been found that the case mortality may be

greater at certain seasons of the year, but this may depend on factors other than the organism.

(b) *Trauma*.—In the case of disorders due to trauma the exact nature of the injury often influences the rate of recovery. A simple fracture heals more readily than a compound one. A crushed nerve which retains its continuity will recover more rapidly and will give a better functional result than one in which complete division has occurred. Much bruising or damage of tissues will delay restoration to normal, and thermal injuries heal more slowly than others of similar extent.

(c) *Cancer*.—Where a cancer cannot be eradicated or destroyed by radiation, prognosis will be restricted to an estimation of the expectation of life. A knowledge of the type of growth is sometimes of importance because some cancers grow slowly, others advance rapidly and are prone to metastasise, while in certain types spontaneous cure is not altogether unknown. Account must also be taken of the site of the lesion, for those which cause obstruction of some vital channel will run a shorter course.

#### THE DISEASE OR INJURY—THE REACTION TO THE CAUSAL AGENT

So far we have dealt with the soil and the seed, and now we have to consider the effects of their interaction. Disease may be regarded as the action of an agent on the body and the local and distant reactions which follow.

Some diseases are inevitably fatal (tuberculous meningitis), others almost invariably trivial. Some run a short acute course, others drag on into chronicity while still others relapse or recur. Even in the case of a single disease great variations may be found. The average expectation of life after disseminated sclerosis has become manifest is about ten years; fulminating cases may succumb within a few months while chronic cases have been known to survive as long as twenty years. Such individual variation makes prognosis difficult. A disease may be mild, average or severe and the prognosis in general will correspond. A minor attack may scarcely upset a patient, while an overwhelming infection may run a rapid course to a fatal termination. When considering the prognosis, great weight would naturally be given to the *severity* of the disease in the patient. In cerebral hæmorrhage, the deeper the coma and the longer its duration the graver the outlook, and the longer the interval before any muscular power returns the less perfect will be the final recovery. In acute infections the occurrence of septicæmia or of petechial rashes is to be viewed with grave concern. It must be remembered, however, that the apparent severity of an acute disease does not always imply a poor prognosis. A sharp fever or a high leucocytosis may indicate a vigorous reaction. Many conditions which seem to be very severe at the onset may quickly take a turn for the better. Consider, for

example, acute nephritis with virtual suppression, or early diabetes with great glycosuria and even acetonuria, when these are promptly brought under treatment. In acute cases such as these, judgment should be reserved so as to avoid having to give a grave prognosis which will almost certainly have to be revised in a short time. On the other hand, certain infections which at first appear mild and likely to follow a simple course, may later take a graver turn which may endanger life. Serious complications of scarlet fever, for example, may develop in cases apparently benign. Sudden death may occur shortly after what appeared to be a rather slight coronary thrombosis. Such considerations would warrant caution and would suggest that in acute conditions it is unwise to make any firm pronouncement as to the future. The severity of the disease is a safer guide in chronic disorders.

*Extent of Pathology.*—In general, the larger or more widespread the lesion the more severe will be its effects. A large ulcer will take longer to heal than a small one; tuberculosis of both lungs is more serious than when only one is diseased. Similarly a double pneumonia is a graver risk than involvement of a single lobe, and for some curious reason an apical pneumonia is more serious than one in the lower lobes.

The character of the *onset* of a disease may sometimes give information of prognostic value. A cerebral hæmorrhage which occurs during violent exertion may warrant a better prognosis than one coming on during rest.

The *rate of progress* of the disease may often give an indication of the probable duration of the illness.

The *frequency of recurring attacks* should be noted in such disorders as angina, asthma and epilepsy. As a general rule the more numerous the attacks the poorer the prognosis.

*Clinical tests* such as we possess for the measurement of disturbed function are not of great value in forming a prognosis, since most of them merely indicate the state of affairs at the time of testing. In chronic disorders, however, unfavourable tests are often of great importance, though in acute conditions they may have little significance. A high blood urea nitrogen is a serious finding in chronic renal disease, but in prostatic obstruction, or even in acute nephritis, it may be temporary and negligible. Such tests must always be evaluated with due regard to the clinical circumstances of the case.

Clinical tests are usually of more value for prognosis when they are repeated after an interval, since they will then show the trend of the disease and its rate of progress. The blood sedimentation rate, for example, is chiefly used as a measure of improvement and seems to supply information otherwise unobtainable.

The leucocyte count is often of service in acute infections. In pneumonia a good leucocytosis of twenty to thirty thousand is considered favourable; a low count may indicate an absence of reaction

which augurs badly for the patient; a sudden fall in the W.B.C. without concomitant clinical improvement may indicate failing defences.

*General Effects.*—Such measurable factors as temperature, pulse rate, respiratory rate and blood pressure often give information of prognostic value as well as an estimate of the severity of the condition.

A high temperature in a child is of less significance than in an adult. Intractable hyperpyrexia is usually fatal. A relatively low temperature in the course of a fever may indicate a poor reaction especially if there is also evidence of severe toxæmia. A rising temperature after the second or third day in cerebral hæmorrhage is a grave sign; and a continuously rising temperature is often a prelude to death. A sudden and pronounced fall of temperature without clinical improvement is also a bad sign.

Persistent tachycardia after subsidence of a fever may forecast a prolonged convalescence.

In general, the higher the respiratory rate in pneumonia the more serious the condition, and when it is over 50 the outlook is very bad. A constantly falling blood pressure from a previously high level is an ominous sign in apoplexy.

Information of prognostic value may often be obtained from physical examination of the vital organs even when they are not primarily involved. A healthy state of the circulatory apparatus, kidneys, lungs, alimentary canal and cerebrum is necessary for an average prognosis, and any departure from this may aggravate the prognosis. Cardiac dilatation, with a rapid, feeble or irregular pulse, may indicate a failing myocardium, and is of serious import in coronary thrombosis, pneumonia and delirium tremens. A poor digestion is unfavourable in alcoholism and in chronic nephritis. A freely acting bowel is desirable at the beginning of a fever. Delirium may mean nothing more than temporary intoxication, or it may be a warning of unsuspected severity of the disease. Sleeplessness in fevers is usually unfavourable; it is said that if a case of pneumonia has two consecutive sleepless nights recovery is unlikely.

Useful information as to the severity of the illness may be gained by close observation of the patient. The decubitus or attitude in bed may be instructive. A severely ill patient tends to lie flat on his back making little general movement; if he has strength enough to turn on his side the outlook is better.

An *ominous* significance attends such signs as coma, subsultus tendinum and floccitatio, a weakened voice altered in tone, the typhoid state, increasing helplessness, the sunken eyes of dehydration, an expressionless face, the facies Hippocratica, a livid pallor, stertor, hurried irregular breathing, Cheyne-Stokes respiration, disappearance of the cough reflex, hiccough in certain cases, prune-juice spit in pneumonia, a disorderly racing pulse and a falling blood pressure, meteorism or tympanites, extreme emaciation with weakening of all

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## NOTES

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# Ribena therapy in infant welfare

The administration of vitamin C to infants has become a routine feature in child welfare. During the war, scarcity of orange juice was counter-balanced with excellent results by the use of other sources of the vitamin natural to Britain, notably blackcurrant juice, which the Ministry of Food approved as a particularly satisfactory alternative.

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the organs including the heart, acute bedsores, and acidosis in chronic nephritis. All these are unwelcome portents.

The *psychological reaction* to disease has often an important bearing on the outcome. Fear, anxiety, and mental strain are depressing emotions; worry and excitement may have an adverse effect; and depression or lack of interest may be aggravating factors. Cheerfulness and hope are usually helpful.

*Complications.*—What we call complications may be merely an extension of the original disease, or may be some secondary or super-added disorder such as pneumonia or cardiac failure. In either case the new development requires a re-assessment of the patient's condition. Usually the complication adds to the gravity of the case.

Sometimes, however, the new disorder has a beneficial action. An acute infection may benefit a case of asthma or chronic arthritis, and an attack of malaria leads to improvement in general paralysis.

The development of herpes in a case of pneumonia is regarded as a favourable sign.

### THE DOCTOR AND HIS TREATMENT

Professional skill counts for much in prognosis. It will go without saying that an efficient, well-trained and conscientious doctor should be able to produce the best results. Assuming that he has arrived at a correct diagnosis, and has instituted the proper treatment, he should have a good idea of the probable course of events. In many cases, however, it is not possible to reach an absolute diagnosis, but even then a skilful practitioner will not be at a loss, for a careful assessment of the general condition will often give a fair indication of the probable outcome.

During the course of the illness the doctor should note the rate and direction of progress, and he should be constantly on the look-out for new developments. From his knowledge of the normal course of the disease, he will take steps to guard against possible dangers and complications—for example, the development of bedsores or urinary infection in paraplegia, of dehydration in severe diarrhoea, of alkalosis in obstructive vomiting, of ketosis in uncontrolled diabetes, or of perforation or hæmorrhage in typhoid. Such dangers will be foreseen and avoided or counteracted.

Sound *treatment* intelligently applied improves prognosis, and in some cases may alter it entirely. Many disorders formerly inevitably fatal may be controlled or cured by modern therapy. The neurosurgeon may save a doomed life by removing a brain tumour; prompt action will control diabetic coma.\* In lesser degree, quinine will put an end to recurring attacks of ague, and salicylates to the fever, pains and swellings of rheumatic fever. With modern resources

\* It is interesting to find that so eminent a physician as Dyce Duckworth recorded in 1896 that he had never seen a case of diabetic coma recover.



disease may be shortened, its immediate effects mitigated, permanent disability avoided and sometimes the full expectation of life may be restored. Skilled nursing, hospital facilities and the ever-increasing resources of chemotherapy will improve the patient's chances, while massage, occupational therapy and rehabilitation will do much to hasten economic recovery and reduce permanent disability. On the other hand, many factors may interfere with the attainment of maximum results—poverty, with its accompaniment of bad environment and poor feeding, carelessness and even lack of co-operation on the part of the patient. The dangers of inadequate treatment are too obvious to need emphasis.

If, while under treatment, the patient fails to respond as is expected the whole position must be reviewed and the diagnosis reconsidered.

Whether there exists a specific therapy or not, much depends on the personality of the doctor himself; a man with a cheerful, faith-inspiring manner will do more for the patient than a hesitating, gloomy pessimist. The ability of a doctor to inspire confidence in his treatment and in himself is a powerful aid to recovery.

What the doctor tells and how he tells it may influence prognosis. The interests of three parties have to be considered: the patient's, his friends', and those of the doctor himself. It is well to recognise that knowledge of the possible trend of events is important to the patient as well as to the doctor. The medical attendant should be ready to answer questions at any time, and so avoid being caught unprepared, for much may depend on the manner in which the information is conveyed. In general it will be admitted that the patient has a right to share the doctor's knowledge, but how much should be divulged will depend on the circumstances of the case.

No difficulty will arise in the case of a simple condition where the prognosis is reasonably good. If, however, in such a case there is even a possibility of some adverse development, the doctor may be as well to safeguard himself by adding some such qualifying phrase as "provided no complication arises."

Where the diagnosis is uncertain, the prognosis should be given only in the most general terms. Sometimes the patient may be so little affected by the illness that a good prognosis is justified, or again, it may be perfectly obvious that whatever the condition may be he is so seriously ill that death is inevitable.

Difficulty arises in deciding how much to tell when the case is serious or almost certainly fatal, or where the patient is already so dangerously ill that an adverse prognosis might do him harm. In grave or hopeless cases there is a tendency to withhold information, not because the inevitable death sentence is unpleasant, but for fear of its effect on the patient or his friends. To mention a diagnosis of cancer or angina is really tantamount to reading a death warrant, since the layman fully appreciates the prognostic significance. The cautious doctor will remember that there is always a chance that a

diagnosis may be wrong ; even experts and X-rays may fail, and the best diagnostic skill may sometimes be at fault.

The patient himself has often a good idea of the seriousness of his illness, and the final verdict, though unfavourable, may be welcomed as a relief from the haunting fear of uncertainty. Probably few people are really afraid to die when it is apparent that their time has come. Or again, the patient may be so distressed with pain and weakness that the intimation of impending death may give promise of a happy release. How the ill news is conveyed may be more important than the news itself. Before saying anything to the patient, the doctor should carefully consider his personality, and should make an estimate of how the information is likely to affect him. Tact and consideration may cover an unpleasant verdict. Few doctors will be prepared to state the brutal truth even if the patient has said, "Is it cancer? I can stand it." The shock of a bluntly stated verdict may so depress the patient that he loses all hope and goes downhill rapidly. Often it is possible to soften the blow. Sometimes a definite reply can be avoided altogether, and eventually the unpleasant fact will dawn upon the patient.

In certain cases, especially in chronic disorders, the future will depend largely on the attitude of the patient himself, and it may be necessary to be brutally frank in order to frighten him out of his complacency, so that he may come to see the importance of taking proper care of himself. This question may arise in cases of hypertension or chronic nephritis.

There is also the problem of the accidentally discovered lesion which is not yet causing trouble. Should the patient be told of a fully compensated cardiac murmur or the presence of a silent gallstone?

What information is to be given to the patient's friends matters most when the illness is serious or desperate. In such cases the whole truth must be told to someone. Whatever may have been withheld from the patient, it is necessary for everyone's sake that one of the relatives, the most responsible and discreet, should be taken into the fullest confidence of the doctor. This safeguards the doctor, and allows the relatives to make any necessary arrangements. Timely warning of any possible danger must always be given to some responsible person.

It is unwise to give a good report to the patient and a bad one to the relatives for, even though they do not tell, they may betray the true state of affairs by their manner or reactions. Even when the outlook appears desperate, care must be taken not to destroy the last ray of hope or to allow the ministering friends to become discouraged in the hopeless fight. An atmosphere of hope and optimism is most favourable to recovery.

The doctor, after making certain of all the facts, should consider the whole position with the greatest care, and then should give his opinion clearly and frankly so that no misunderstanding is possible. Hesitation creates suspicion ; evasion and reticence will suggest that

something is being held back, and an observant patient will be quick to notice such things. An unconscious sigh or an unguarded word may belie the stated opinion. Care should be taken not to cause alarm by speculating on things which may never happen. Many diseases are so variable that it is impossible to be definite in framing the prognosis. Estimates as to the length of time the illness will last should be specially safeguarded, though it is usually necessary to suggest some approximate period. Similar caution must be observed in considering the degree of certainty that any event may happen; even in the most straightforward cases it is well to avoid such words as "always" and "never."

The doctor should be as optimistic as circumstances will allow; he should inspire good hope and should encourage the patient and his friends. If error is possible it should be on the side of a good prognosis, for that is always better than a bad one which is not fulfilled.

Whatever the circumstances, the actions of the doctor will be guided solely by the welfare of the patient.

## THE RESULT OF ARTHROPLASTY OF THE ELBOW JOINT AFTER THIRTY-TWO YEARS

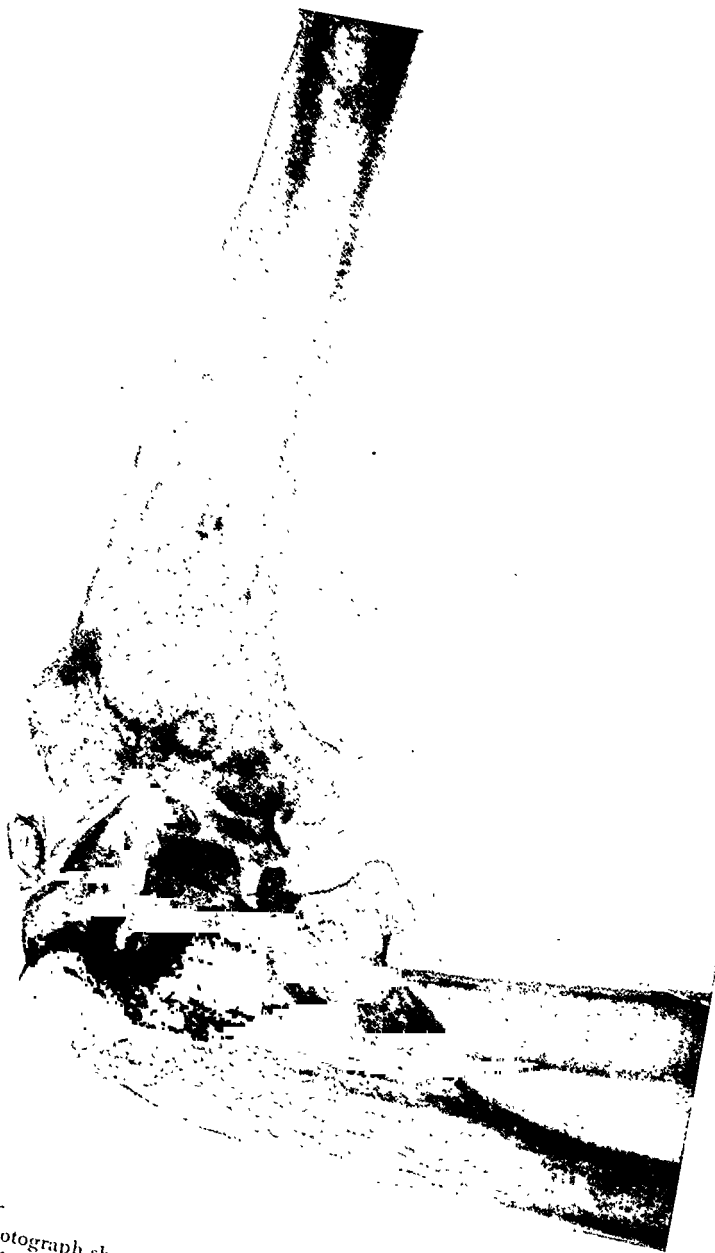
By G. GREY TURNER

IN the *Edinburgh Medical Journal* for May 1914 I published a Clinical Record under the title of "A Case of Arthroplasty for Bony Anchylosis of the Elbow Joint followed by a Good Result in spite of Infection." In order to appreciate the interest and significance of the after-history of this case it is necessary to briefly recount the circumstances of the early stages and some details of the operation as there recorded.

The condition was the result of infective osteitis of the right humerus secondary to the same condition in the left tibia. When the patient (J. B.) first came under my care in October of 1911 he was a rather flabby lanky lad, aged eighteen, and the condition was of twelve months' standing. Both affected bones were much thickened and there were sinuses, the result of sequestra, which were removed from both leg and arm. It was nearly two years before the necessary incisions and the sinuses finally healed. At the expiration of this time the general condition was much improved and the lad was in fair health though still a little anæmic. The right elbow was firmly ankylosed by bone in almost full extension with the forearm fixed in pronation. The upper arm was very much wasted but the forearm muscles were well developed and strong. The region of the elbow joint was thickened, the skin being tightly stretched over the bony points to which it was adherent. The operation of Arthroplasty was carried out and the condition found is sufficiently indicated by the published note: "Exposing the bone was a matter of no small difficulty on account of the adherence of the skin to the underlying parts and of the fibrous condition of the muscles. What remained of the capsule was intimately blended with the other structures. After clearing the posterior surface of the humerus and exposing the ulnar nerve, the joint-line was attacked with hammer and chisel, the bones being thus separated. During this procedure what appeared to be an active infective focus was found in the lower end of the humerus on the inner side. This was a cavity about the size of a pea, containing granulation tissue and a drop or two of pus. At this stage it appeared to me useless to proceed with the operation of arthroplasty, since absolute asepsis is the first essential for its success. Excision was contemplated, but I finally decided to complete the arthroplasty in the hope that the infection might not be sufficiently active to vitiate the result. The cavity was therefore thoroughly cleaned out with a sharp spoon and the operation was proceeded with. The upper ends of the radius and ulna were now cleared but no attempt was made to open

up the radio-ulnar joint. The lower end of the humerus was rounded off, but no more bone was removed than would allow of the full range of flexion and extension, the operation consisting of an opening up and remodelling of the joint, and being in no sense an excision. It was only found possible to cover a small part of the inner aspect of the joint surface with the remains of the capsule, which was fixed in position by a few points of catgut suture. This still left the greater part of the bones uncovered, and a flap of fascia lata, about two inches square, was therefore taken together with some subcutaneous fat from below the level of the bursa over the great trochanter, and this provided an ample covering for the remainder of the humerus. It was fixed in position with catgut sutures and the posterior muscles drawn together over the joint. The skin, which had been buttonholed in one or two places, was sutured and the arm put up in full extension, as this seemed the position in which there was least chance of displacing the flap of fascia."

After the operation the lad suffered a great deal of pain and the parts were obviously infected, the old sepsis having been urged into activity. There was suppuration with an abscess on the inner side of the humerus which had to be opened. Five weeks after the operation there was still active infection with a septic looking granulating wound over the outer condyle of the humerus about the size of half-a-crown and a granulating wound twice that size over the olecranon. There was also general swelling and continued pyrexia which made me despair of a useful result, recurrence of the ankylosis seeming to be inevitable. For that reason the arm was put up in flexion so that it would at least be in a useful position for a stiff elbow. As a result of this manipulation the wound still further separated so that the olecranon was exposed to an alarming extent. But in spite of these troubles the wounds healed and movement steadily improved. When seen nine weeks after the operation it was found that the patient could almost straighten the arm so that both flexion and extension were very satisfactory. Thereafter he continued to make good progress though there were one or two outbursts of infection in connection with the old focus in the arm. After some months he returned to work as a foyboat man which meant rowing or sculling about the river Tyne in all weathers and at any time of day or night, and also involved handling heavy ropes. Six years after operation we got him fitted out with a new boat which he not inappropriately christened "Success." Thereafter I lost sight of my patient but was delighted to hear from him again in December 1946, just thirty-two years after the inauspicious arthroplasty turned out so satisfactorily. Ever since he restarted work he had continued to follow his occupation on the river until the outbreak of the war in 1939, when he found it more advantageous to take up the work of a dock labourer. Since the uneasy peace, slackness of work has meant loss of employment, but on occasion he is back on the river helping a friend with his boat.



An X-ray photograph showing the condition of the elbow-joint thirty-two years after Arthroplasty. Flexion and extension are complete.



At the Newcastle Infirmary he was seen recently and examined by Mr Norman Hodgson who had an X-ray taken which is here reproduced. It shows how near the joint surfaces are together and demonstrates that without interposition of the fascial barrier bony union must have been inevitable. The osteophytes were present at the time of the original operation. When I examined the patient in January of 1947 I found that at fifty-two years of age, and thirty-two years after the arthroplasty, he is well nourished and strong. The joint looks unstable and in the absence of muscular effort there is marked lateral mobility. The upper arm is very thin as though the humerus was merely clothed by little else than skin, but what muscle remains is well developed for full flexion and extension are not only present but powerful, so that the joint in action is very strong. Further, these movements are carried out smoothly without any pain or creaking to suggest arthritic changes. The forearm muscles are particularly well developed. The upper radio-ulnar joint is ankylosed by bone for there is no independent movement there, and supination is brought about by rotation of the humerus. The arthroplasty in this case was carried out as I had seen Murphy of Chicago do it in 1906, when at the height of his fame he expressed great faith in the method. The satisfactory result here recorded so long after the intervention applies the test of time and is a vindication of the value of arthroplasty in some cases. The original paper was illustrated by photographs and X-rays of the patient. It is regrettable that bacteriological examinations were not then made.



## THE RÔLE OF THE GENERAL PRACTITIONER IN FUTURE MIDWIFERY PRACTICE \*

By J. BRUCE DEWAR, M.B., F.R.C.S.Ed., M.R.C.O.G.

DURING the last hundred years there has occurred, albeit gradually and at times unnoticed, an uninterrupted evolution in the practice of midwifery. In each successive stage the general practitioner has played his part and it will be of advantage to trace the major phases of this evolution, since in so doing the rôle of the general practitioner in future midwifery practice will become more apparent.

A century ago the practitioner, and I use this term in contradistinction to the specialist obstetrician, found himself an isolated member of obstetric society, with by modern standards a very brief training in midwifery; and, since the parturient, without the benefits of ante-natal care, was throughout the major portion of society left to the attentions of untrained handywomen, his services were most usually called for in the presence of difficulty. The sole armamentarium of these "Sarah Gamps" was as often as not a liberal supply of spiritous liquor, and, lacking any form of training, they had perforce to pick up such rudiments of practice as they could glean from tavern gossip mingled with natural shrewdness and powers of observation, while under their mellowed direction the labour was conducted in a manner prescribed by tradition and superstition.

The practitioner thus on many occasions found himself confronted with a tired and exhausted patient, doomed by the interference of ignorance and already manifesting the flush of the dreaded "child-bed fever." Isolated as he found himself, lacking the modern means of communication and transport, and denied the ready services of specialist and hospital, he had no alternative but to rely on his hard-won experience, gained not infrequently at the expense of mother and child. In the germ-ridden and unsanitary domicile of the period he had to attempt the impossible, and small wonder that under such conditions catastrophe frequently resulted; maternal and foetal deaths which to-day would be considered essentially preventible, and women left permanently scarred and prematurely aged, victims of an age of ignorance and superstition.

Let us who practise in the more kindly era of asepsis and prophylaxis, reflect in all humility on the many gifted and courageous pioneers, who, lacking the manifest advantages we presently enjoy, yet so conducted the practice of midwifery as to earn for themselves, and for us, the respect and confidence of womankind.

\* Edinburgh Obstetrical Society, 99th Session Meeting held on 11th December 1946.

As time progressed the handywoman was superseded by the midwife, graduated from a teaching centre after a term of supervised instruction, and she carried with her into the field the most up-to-date methods of her time. Already in her practice began the elements of ante-natal care while labour was conducted under her direction on the disciplined principles of the training school. Maternity bed accommodation, although insufficient, was instituted in the larger cities, and the principles of antisepsis and asepsis spread throughout midwifery practice.

With further progress the midwife engaged in individual practice was largely replaced by the local authority midwifery service, both in town and country, or by the district nurse. Ante-Natal Clinics were opened in increasing numbers and maternity hospitals established in more extended areas, relieving to a degree a growing demand for ante-natal and lying-in accommodation. By degrees undergraduate teaching of midwifery was intensified so that the neophyte practitioner entered practice with a training in midwifery never achieved by his predecessors.

And what of the practitioner who brought with him into practice the fruits of research and more generous teaching? In no time he found his high ideals shattered in the miner's row, the shepherd's bothy or the dockside hovel. With bitterness he viewed the wide gulf that separated the wards and theatres of his training hospital from the primitive and often unsavoury conditions of industrial domiciliary midwifery. Many were the demands of general practice on his time and energy, and can we blame him when he slipped into the more cynical outlook of his senior colleagues and sought in his midwifery bag the short cut to at least a few hours in bed?—the tenets of his mentors being remembered as all very well in the sheltered purlieus of hospital but impracticable in the hurly burly of general practice.

Thus, while his instruction surpassed that of his predecessors, he found himself a victim of his environment with a living to make, and in that living he found midwifery a necessary evil, time consuming and poorly remunerated. It is not without significance that practices are from time to time advertised with the special attraction of "no midwifery."

Let us now consider the state of affairs as exist at the present time. Maternity hospital provision throughout the country, both for the normal and abnormal case, although still inadequate, has never been greater. Clinic and ambulance services, the latter by air as well as road, have reached a high degree of organisation; with the introduction of the Maternity Services (Scotland) Act, 1937, every pregnant woman can obtain the service of a practitioner, who has in turn a guaranteed recompense where previously on occasion none was forthcoming, as well as the backing of a hospital and consultant service.

At no time in the history of midwifery practice has integration

been so fully achieved and yet even before the outbreak of the Second World War there was a definite swing of the pendulum from domiciliary to institutional midwifery. The exigencies of a nation at war coupled with an ever-increasing shortage of civilian practitioners accelerated this trend to the institution.

I am of the firm opinion that, with the never really satisfactory conditions of domiciliary midwifery in a country half of whose population are living in outmoded and cramped dwellings, and with the present acute housing shortage, so far being solved to the satisfaction of a few by pamphlet and computation in preference to brick and lime, institutional midwifery has come to stay. Evidence of this from every quarter is not lacking.

And now as to the rôle of the general practitioner in future midwifery practice. In my experience I have found, as regards midwifery, three distinct types of general practitioner. The first abhors midwifery and has avoided it at all times, the economic status of his practice so permitting. The second conducted an unwilling midwifery practice either because there was no one else to do it or competitive practice made it imperative. The third, most often, but not always, a former obstetric house surgeon, is both interested and keen on midwifery and welcomes the opportunity to practise it.

The first type automatically removes himself from the present discussion, while the second, by virtue of the organisation now in force, can and does hand over as much of his midwifery practice as is possible to hospital and specialist. It is with the third type and his future that we are concerned.

It is estimated that about 70 per cent. of all births will in the future take place in hospitals, central and peripheral. Similarly, when impending legislation becomes effective, it is not unreasonable to expect about as high a percentage of practitioners will gratefully hand over the burden of midwifery to a national maternity service. The remaining practitioner, the third type aforementioned, will still have the opportunity of elective and selective midwifery practice.

As an earnest of his keenness and interest it should be asked of him that he returns to his teaching school for a more extensive post-graduate training than time in an already crowded undergraduate syllabus permitted. This eminently logical step has already been advocated by the Royal College of Obstetricians and Gynæcologists in their "Report on a National Maternity Service," and while its critics have raised the red herring of an obstetrical hierarchy, it is to be borne in mind that the self-same Royal College of Obstetricians and Gynæcologists has for years granted, after prescribed post-graduate training and examination, a Diploma in Obstetrics to encourage the keen practitioner to acquire the hallmark of competence.

At once the critic again asks a question: "Why trouble to teach obstetrics to the undergraduate if in the future only a selected number will so practise?" The answer surely is that it is very necessary still

to continue the basic teaching in all branches of medicine since the graduate, entering whatever branch of medical practice, may in special and unpremeditated circumstances be called upon to recognise and deal with any emergency of whatever nature, be his responsibility no greater than the securing of appropriate aid.

In their report the Royal College of Obstetricians and Gynæcologists, with reference to postgraduate training, make comment as follows: "We believe that this principle should hold good for general practitioners who attend confinements in local maternity centres and patients' homes, and who take midwives' aid calls, but also for those who do ante-natal work, whether in special ante-natal clinics or health centres."

In specifying the rôle of the practitioner in the future, the Report goes on to state: "The important share that general practitioners would take in the Service would thus be to have charge of beds at the local maternity centres, to do ante-natal work at ante-natal clinics and at health centres, to do domiciliary midwifery themselves and to take medical aid calls from midwives. To achieve the true and desirable team spirit, integration of the work of the personnel is a paramount necessity, and we know of no better way of making a general practitioner feel that he is a member of the team than of giving him the opportunity of being for periods of time closely associated with the work of the large centres."

In conclusion I would, therefore, venture to prophesy that for the practitioner who desires, through interest untrammelled by necessity, to practise midwifery there will exist ample opportunity to take a full part, as a welcome member of a team, in a maternity service of the future, and under satisfying conditions such as his predecessors have never enjoyed; a maternity service which by its very comprehensiveness and efficiency will earn the envy and admiration of the civilised world.

By A. FRASER LEE, M.C., M.D.

THIS subject ought to produce an interesting and profitable discussion. I quite frankly hold that in the practice of midwifery, the general practitioner, engaged in family practice can, if he chooses, make this branch of medical work peculiarly his own.

In the last forty years there have been enormous changes in general practice and in specialist practice.

When I was a student (I graduated in 1907) there were distinguished men who were both surgeons and physicians. There were consulting, teaching physicians, actively engaged in all branches of general practice. Now, and quite rightly, all major surgery is outside the scope of general practice. Pure medicine is also now so complicated and specialised that the general practitioner has also had to hand over to the medical specialists a great amount of his work.

Fevers, orthopædic surgery, venereal disease, ear, nose and throat, eyes, gynæcology, are all now highly specialised subjects and the general practitioner must, in justice to his patient, make his initial diagnosis and proceed to hand over the case.

But if he chooses midwifery practice many still remain in his hands, and if he trains himself for it he ought to be the predominant partner in midwifery practice in the future. It is essential, however, that the general practitioner is not pitchforked into the practice of midwifery without sufficient practical training.

No graduate who acquires his degree is expected to perform a major surgical operation on the following day ; but in the past, young graduates going into practice have had to attempt manipulative midwifery work of which they were entirely practically ignorant, though theoretically efficiently trained. I would venture to suggest that no young graduate in the future should engage in midwifery practice until he shows a higher academic degree in the subject and also produces evidence of practical experience acquired as resident in a maternity hospital. Is that quite Utopian and fantastic? I don't think so.

There are many graduates who definitely would not desire to pursue midwifery as a special subject. The future specialists in all branches of the profession, the men who are going into the Public Health Service, or the Naval, Army or Air Force Service, would reduce the number of those requiring special midwifery training to a figure which our teaching hospitals could reasonably overtake.

The ordinary daily routine work of the general practitioner ought, if he has acquired sufficient practical training in midwifery, to make this branch of medicine his own special subject.

#### ANTE-NATAL CARE

We in general practice must have an all-round if often very superficial knowledge of general diagnosis. If we are trained in ante-natal care, we ought to be the best qualified men in the profession to carry it out. We know our patients. It should certainly be possible to train the practitioner to undertake the ante-natal care of all pregnant women. In case of difficulty or doubt, he would have behind him the more specialised skill of the consulting teaching obstetrician.

Another point I would like to make quite clear is that midwifery work in general practice is now much easier and infinitely less irksome to practise than it was forty years ago. Then it was quite a common occurrence for the practitioner to be summoned by his patient at the commencement of labour—never having seen her before. He was expected to remain in close attendance during the long first stage of labour and remain with his patient until delivery was completed. Fortunately ante-natal care has changed all this, and also the increasing numbers of patients who are now delivered in institutions and nursing

homes has made the time to be spent in attendance by the general practitioner very much less.

X-ray diagnosis in cases where clinical diagnosis is difficult has been of immense value in practice. The occipito-posterior position, for example, can now be definitely diagnosed by X-ray, although previously it was very often missed until labour was well advanced. There are, of course, still a certain number of cases which require hospital treatment during their pregnancy. Hyperemesis, the toxæmias of pregnancy of varying degree, should in most cases be handed on for hospital treatment and investigation by the consultant obstetrician.

The next point I would raise is the question of the presence of the general practitioner at the actual delivery. I have very definite views on this point, borne out by my own practical experience. If the doctor is in attendance, it gives his patient more confidence and is a comfort to her. Again, no one can be absolutely certain until after the delivery of the placenta that a confinement is to be absolutely normal, *e.g.* a very tight cord round the child's neck, difficulty with the delivery of shoulders, an unexpected but possible post-partum hæmorrhage, the fortunately much rarer development of post-partum shock, the necessity for the insertion of a couple of stitches, are just some of the reasons why, whenever possible, the doctor's presence at the actual delivery is desirable and important. I think the fact that most medical men always arrange for a doctor to be in attendance at their wives' or daughters' confinements confirms my own strongly held opinion on this matter. It is of course quite unnecessary to be in constant attendance throughout the labour, and here I think the general practitioner can claim to be the member of the profession to conduct this work with less interference with his other duties. He can leave the case to pay other visits and return. The gynæcologist has not this advantage in his obstetric work. His day is much more definitely arranged for him, and any "hold up" by a midwifery case may interfere seriously with his operating work or his teaching duties. But it is amazing how seldom, for instance, I have had to miss my consulting hour for a midwifery case, and on the occasions when this has happened, the patients return at the evening hour or next day and are by no means unduly perturbed or upset.

The care of the mother in the puerperium should present no great difficulty to a trained general practitioner. The all-important post-natal visit and examination can be fitted into his day's visiting list seven to eight weeks after the confinement without any inconvenience.

There is one department of this work in which, perhaps, we older practitioners are behind our younger colleagues. That is, in the care and feeding of the infant. I confess I am myself very much in the hands of the trained nurse or even the old nanny in this really important subject. Proper training for us practitioners in the care and management of the infant would further strengthen our claim to conduct midwifery work. A post-graduate class on infant feeding and the

proper diet for the young child would find, even an old graduate like myself, "knocking at the door." We older practitioners, perhaps, do not fall so easily into the wiles of the traveller for proprietary drugs, but I think the infant food merchants find us an easy prey.

Now, may I just summarise what exactly I expect the general practitioner in midwifery in the future will be able to perform?

*Proper Ante-natal Care.*—He should be able to measure a pelvis; to diagnose the relative size of the head to the pelvis and then, if he is in doubt, he should call in a consultant obstetrician three weeks before the onset of labour and consult as to the proper conduct of the case.

He should be able to perform external version and to diagnose position, getting an X-ray picture if in doubt. In the actual delivery of the patient he should be properly trained in the use of forceps. He should be able to deliver a breech; to manually rotate an occipito-posterior position; to perform internal version if required, and be able to manually remove an adherent placenta and to deal with post-partum hæmorrhage.

What will he not be expected to do? Any midwifery requiring abdominal surgery. That must always remain in the hands of the gynæcologists and consultant obstetricians.

Then, you may say, what is left of midwifery work for the consultant obstetrician? All the teaching of this important branch of medicine. All the research work in this important branch of medicine; and is there not much land still left to be possessed? A close liaison between the general practitioner in the outpost of medicine and the teachers in the hospitals should be established. A sufficiency of small homes and hospitals both in city, town and country should be provided in the future where the general practitioner trained in midwifery will be able to carry on his work.

Midwifery, in my opinion, is the real corner-stone of a happy general practice. Your patient is suffering from acute appendicitis or a ruptured, duodenal ulcer. He is grateful to you for your successful diagnosis, but would really have preferred to have escaped the ordeal. Your medical case with pneumonia, treated successfully, is grateful, but would have preferred not to have had pneumonia. But, by and large, in your midwifery work your patient and her husband are grateful to you for your care and are proud of their first-born son or daughter, and, to use a Scots expression, the family are thirled to you.

Then, from the family doctor's point of view, the delight of looking after the children, watching them through school, often advising as to their future, hearing of their progress and, as unfortunately at my age I am doing now, finally producing for them their first-born sons and daughters, makes general practice well worth while.

I confess I am an unscientific man, with only my clinical interests. I have found, however, in general practice an amazingly interesting life. It would have lacked a great deal of its interest and pleasure if the practice of midwifery had been taken out of my hands.

## DISCUSSION

*Dr Hector MacLennan* said how delightful it was to hear Dr Fraser Lee's views, and that if all general practitioners held similar views there would be no reason for the discussion which was being embarked upon. He was made anxious to think, however, that a general practitioner might still feel impelled to undertake on his own a delivery involving what might be regarded as a major obstetrical operation. Dr Fraser Lee was prepared to do an internal version or to deliver a primigravid breech, but would avoid abdominal surgery. Of those alternatives, caesarean section was by far the easier. Dr MacLennan had seen more than one accomplished obstetrician in grave difficulties in conducting a primigravid breech delivery, and breech delivery should only be tackled by a general practitioner in an emergency.

So far as Dr Bruce Dewar's contribution was concerned, Dr MacLennan agreed with practically all of it, except with regard to the desirability of increased institutional midwifery. At the moment it was a necessity because of lack of adequate housing, but he hoped that in the future there would be a swing of the pendulum again, and that patients might be allowed to have their babies in the pleasantest atmosphere, namely, in the "bosom of their families."

*Dr Davidson* (Kelso) said that he and his partner had found that since they had started midwifery practice in hospital they had been able to do what they would have found difficult in the home. The problem of removing retained placenta was one of the biggest difficulties in domiciliary midwifery. In a patient's house it was an extremely difficult proposition, but sometimes it was too far for the patient to come to hospital, so the doctor must deal with it at home.

*Dr Somerville* (Bonnyrigg) agreed that "midwifery is one of the nicest parts of a general practitioner's work." The best atmosphere for a baby to be born in was at home. With ante-natal work carefully done these major difficulties at the actual birth should be few, although no one could tell when he would have to deal with an adherent placenta, relying not on asepsis but on antiseptics.

The greatest difference he had noticed since 1914 when he had started at home had been the change from the "dangerous handywoman" to the trained nurse. In his area the Maternity Services (Scotland) Act, 1937 had been a godsend to doctors whose proper position had been stated under that Act. Through the operation of this Act he could get all the help he wanted, could get the patient X-rayed, or admitted to hospital. Under the National Health Service he was not quite sure what was going to happen, but he hoped it would not interfere with the good work, but would help in other ways.

*Dr Sturrock*, in thanking the openers, regretted that they agreed on so many points. The question to be answered seemed to be: Was midwifery practice by general practitioners to be restricted to those who had had special post-graduate resident training in recognised maternity hospitals, or, as is the present custom, was every graduate to be allowed, should he so desire, to carry on midwifery practice with consultative and institutional services at his back? This was an important point to settle because the whole plan of teaching depended on it. Much benefit had resulted from the extension



and enlargement of undergraduate clinical teaching during the last twenty years. A team spirit had been fostered and the limitations of domestic midwifery appreciated so that the standard of obstetrics generally had been raised. But if post-graduate training was to be stressed to provide the necessary medical personnel, it would mean a reduction in undergraduate teaching as the present standard would be wasteful of clinical material and teaching time.

*The Secretary* then read a letter from *Dr Eneas Mackenzie* (Tain), in which he said that normal midwifery should be carried out at home under joint control by a general practitioner and a qualified midwife, both of whom had attended the patient ante-natally and both of whom should be present at the delivery. The existing trend towards hospital obstetrics was regrettable, and was to be attributed to bad housing and lack of home helps, and it was wrong to plan for its indefinite continuance. The family practitioner had an unequalled position from his wide general knowledge of medicine, obstetrics, pædiatrics and social background to render him fitted to conduct midwifery practice, while his intimate human contacts provided opportunities for a kindly and humane management of each patient as an individual which was quite lacking in hospital practice. Ante-natal care was best conducted by visits to the patient in her own home. Public ante-natal clinics were undesirable from the psychological standpoint, apprehension being induced both by the general circumstances and by the gossip of other patients.

The teaching of obstetrics had been bad in the past, and present teaching was not much better. There was insufficient emphasis on the conduct of a normal confinement, and the performance of too many episiotomies and cæsarean sections was inculcated.

*Dr Mackenzie* believed that the foundation of future successful midwifery practice was primarily the provision of good homes, and qualified home helps, with a first line of doctors and nurses with wide general training and sympathies. The general practitioner must know his limitations, and must never be ashamed to call for help in time, while specialists must recognise general practitioners as equal colleagues of wide general knowledge and experience. Lastly was required efficient and humane management of hospitals from which mobile teams operated ; and close co-operation between all branches of the service was essential.

*Dr Lewis Owen* (Edinburgh) said that he could not leave unchallenged some of the things which had been said, particularly as regards manual removal of adherent placenta, breech delivery in the primipara, and many cases of version at the patient's home. He was not greatly in love with midwifery, but considered it a very fundamental part of general practice.

There was a great deal wrong with domiciliary midwifery, particularly at present, and he did not agree that the right place was always at home. But there was much wrong with universal institutional midwifery ; even so, he thought the great majority would be better delivered away from home, probably nearer 90 per cent. than the 70 per cent. estimated by *Dr Bruce Dewar*. The rôle of the general practitioner should be more for ante-natal and post-natal care than for actual delivery at home, particularly under present domestic conditions, and he could see no reason why any patients should not be delivered in hospital or a nursing home and brought home soon afterwards.

With regard to the working of the Maternity Services (Scotland) Act, it

did not seem to be doing very well in Edinburgh. Comparatively few doctors had accepted service under the Act. He wondered what was wrong with a scheme which aimed to deliver as many people as possible in their own homes, if so many Edinburgh doctors refused what was really "money for jam." Perhaps this was a temporary phase on account of domiciliary difficulties.

Unlike Dr Fraser Lee, he had found that home midwifery cases interfered very considerably with his working day—very much more than nursing-home cases. In the "boom" shortly after the last war in one year he had had 126 confinements with hardly a whole night in bed, which was not good for any doctor or his patients, nor for the practice of medicine generally.

*Dr G. J. Alexander* (Edinburgh) agreed that the family doctor was the most suitable person to conduct ante-natal care. With regard to the conduct of the labour, in Edinburgh most happy relations existed between general practitioners and all the consultants, and there was no question of the former having to do complicated obstetric operations under difficult conditions. He did not agree that one should do things like removing an adherent placenta single-handed if it was at all possible to get the patient into hospital or nursing home. He had been in the position of having to face up to adherent placenta both in the country, where one had to tackle it alone, and in town where he had no hesitation in getting someone else in. Dr Eneas Mackenzie had said there should always be two people at a confinement, and he agreed with that, saying he considered the ideal was to have a trained nurse and a doctor, but when it came to a forceps delivery, to have a colleague as anæsthetist relieved one of much anxiety.

With regard to the question of nursing home or hospital *versus* the patient's own home, he was inclined, other things being equal, to consider the patient's home as the ideal place. The difficulty was now one of housing and of domestic help. Dr Alexander said he would like to pay tribute to the Queen's Institute of District Nursing, whose nurses had replaced the "Sarah Gamp" of earlier times and had made the most amazing difference to domiciliary midwifery.

*Dr Wilkie Miller* (Edinburgh) agreed that there was a case for increased post-graduate training of general practitioners engaged in obstetrics, but he was firmly opposed to any suggestion that a higher degree in obstetrics should be required from the general practitioner. In the planning of the National Health Service in Scotland, a suggestion to this effect had at one time been adumbrated, since the passage of the appropriate Act would provide *inter alia* opportunities for redrafting the sections of the Midwives' Act, referring to the summoning of medical assistance by midwives. He understood, however, that the intention now was so to redraft these sections as to ensure the free right of any registered medical practitioner to undertake midwifery without any special higher qualification.

*Dr W. I. C. Morris* also spoke.

*The President*, summing up, said that the discussion had been most interesting, and he thanked the openers for their contributions. As Dr Sturrock had stated, it was very important for teachers to know what was going to happen in regard to midwifery in the future; some doctors did not want to do midwifery, and the President considered that these men would never do it well, especially if they were coerced into it. He thought, therefore, that it

was a waste of clinical material to teach all students the same amount of midwifery, and he would suggest that students should have a limited course in the first instance, and those who wished to practice midwifery later should spend six of the twelve months in hospital which was being recommended, before getting their degree, doing midwifery ; then they would get much more practical work than could be given to the students at the present time and would be better fitted to attend midwifery cases.

Dr Somerville had mentioned that he considered the atmosphere of the patient's own home to be the best for a woman's confinement. This was thought to be true in a good many cases, but certainly not in all, as these women could not get away from their home worries which were definitely detrimental to their well-being in the puerperium. He would also assert that no primipara should be delivered in her own home if a hospital or nursing home was available, as one could never tell how a first labour would progress. He would also hospitalise all women having their tenth or subsequent child for the same reason.

The Society was grateful to Dr Mackenzie for his letter ; they all knew him as an enthusiast. He was really one of the white sheep Dr Morris spoke about, and considered that every general practitioner was as white as himself, which was certainly not the case as far as midwifery was concerned. Dr Mackenzie spoke of the dangers of clinics owing to the gossip that went on in them ; this was a very important point as many young mothers were frightened considerably by the stories that they heard at these clinics.

*The President* then called on *Dr Fraser Lee* and *Dr Dewar* to reply.

## THE ACTION OF TOXIC DOSES OF INSULIN ON THE SUPRARENAL MEDULLA IN RABBITS

By Z. Z. GODLOWSKI, M.D.

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REPORTS published in recent years have at least partly established the correlation which exists between insulin and adrenalin action in carbohydrate metabolism. Cannon, McIver and Bliss (1924) brought forward very convincing evidence of the increased adrenalin output which follows the injection of toxic doses of insulin made under various laboratory conditions. Tscherboksaroff *et al.* (1925), Langecker (1925) and many others confirmed Cannon and his co-workers' findings in numerous but differently executed experiments. Further, Elaut (1929-30) and Goormaghtigh (1931) found definite histological evidence of hyperfunction of the suprarenal medulla after the injection of toxic doses of insulin into rabbits and mice. Apart from these laboratory reports, there are some vague clinical observations on the interdependence of bronchial asthma and the function of the suprarenals. Eppinger and Hess (1909), for example, from purely clinical observations, came to the conclusion that bronchial asthma might result from suprarenal insufficiency leading to imbalance between the sympathetic and vagal systems, and through a sympathetic hypoactivity and consequent vagal preponderance, resulting in spasm of the bronchi. Jurasz (1923) observed a slight improvement in his bronchial asthma cases after the application of small doses of X-rays to the region of suprarenal glands. David and Hirsch (1923) showed in rabbits that one skin erythema dose paralyses or diminishes, while one-quarter of this dose stimulates the function of the suprarenal medulla. Wegierko (1937) reported a few cases of bronchial asthma successfully treated with insulin shock.

Insulin shock treatment already has its own history in psychiatry and many reports of this method have been published; Heilbrun *et al.* (1939) estimating the adrenalin concentration in the blood of schizophrenic patients treated by insulin shock, came to the conclusion that lack of response by hypoglycæmic symptoms after massive doses of insulin was due to the outpouring of adrenalin mobilising the glycogen stores and thus replenishing the blood sugar and annulling the hypoglycæmic action of insulin.

Bearing in mind these and many other reports on this subject, I began to investigate the effects of insulin shock on the suprarenal medulla in rabbits in order to try to explain the mechanism of insulin shock treatment in bronchial asthma (Godlowski, 1946).

## METHOD

The animals used for the experiments were 27 rabbits between ten and sixteen months old, of Dutch species and of both sexes. Twelve were used as controls (series A) and were treated in exactly the same way as the experimental animals except for the receipt of insulin; the other 15 were divided into three series of 5 each (B, C and D); all 15 were subjected to the following procedure:—

(1) Standard laboratory diet (all 27 animals).

(2) Every second or third day, after eighteen hours' fast, insulin was injected intravenously in increasing amounts ranging from 20 to 380 units of soluble insulin (B.W. & Co.) per injection, causing hypoglycæmic convulsions; each animal received ten such shocks.

(3) The blood sugar in both the fasting and the "convulsive" specimen was estimated by the Hagedorn-Jensen method; the hypoglycæmic convulsions were arrested by intravenous injection of 3.5 g. of glucose in 25 per cent. aqueous solution and by the subsequent introduction of 50 ml. of 50 per cent. glucose solution by stomach tube.

(4) The rabbits in series B were killed in three days, those in series C fifteen days and those in series D thirty days after their last insulin shock; all were killed by guillotining through the thorax at the level of the diaphragm in order to avoid a possible stimulus to adrenalin production being transmitted from the brain or thoracic sympathetic ganglia through the splanchnic nerves (Emerson and Abreu, 1940).

(5) Both adrenals were removed immediately, cleared of fatty tissue and weighed on an analytical balance; the right gland was put in paraffin, cut serially longitudinally at  $5\ \mu$  and stained by either Giemsa or Heidenhain's iron-hæmatoxylin and van Gieson. Sections stained by Giemsa were used for the measurement of the three axes of the medulla (longitudinal, transverse and dorso-ventral). The longest first and the second axes were found by making serial measurements of each section of the medulla, the dorso-ventral axis by ascertaining the first and last traces of medullary tissue in the whole series and multiplying the number of sections between these points by five (the thickness of each section). The Heidenhain stained sections served for the measurement of the cells and nuclei of the medulla, for a rough estimation of the condition of the blood vessels and the intercolumnar Felicine's canals and intercellular fissures draining the medulla; for counting the number of nuclei and mitotic figures in 1 sq. mm. of medulla and for measuring the areas of the active and inactive medullary zones.

The nuclei and cells were measured in two dimensions by means of a linear ocular micrometer. The average values of 50 cells and 50 nuclei from the active zones and of 50 of each from the inactive zones were taken as the basis for the evaluation of the average size of the cells and nuclei of the whole gland (Drake and Hellwig, 1944).

The morphological criteria of the activity of the cellular elements of the active zones of the medulla were those of Elaut (1929-30), namely, the size of the cells and nuclei, the presence of nucleoli, the presence of granules and vacuoles in the cytoplasm (mitochondria), the shape, size and staining intensity of the endothelial cells of the capillaries and Felicine's canals and the calibre of these vessels as well as of the intercellular fissures of the medulla. The nuclei and the mitotic figures were counted in ten fields of 1 sq. mm., the figures in the corresponding column of the table (pp. 242-3) being averages. The ratio of active and inactive zones was found by estimating the relative area of each type of tissue in a series of random fields of the whole medulla, using a square ocular micrometer. The average values given are based on estimations made on 15-25 sq. mm.

The left gland was used for the estimation of adrenalin by Barker, Eastland and Evers's (1932) method, using Backer and Marrian's (1927) method for the extraction of adrenalin from the glandular tissue. The final reading, however, was carried out on the Spekker Photo-electric Absorbtimeter (made by A. Hilgar Ltd.), using filter Wratten No. 62. In order to obtain more accurate results of the adrenalin concentration, the extract made from the gland was added to an aqueous solution of a known amount of adrenalin; by doing so, the reading was shifted up to a concentration at which even small fluctuations were easier to determine.\*

## RESULTS

During the whole experimental period, the body weight of the animals fluctuated around their initial level. The amount of insulin needed to produce a hypoglycæmic shock varied so widely in individual animals that it was impossible to measure even approximately the shock dose of insulin required.

Since this fact had already been noted by others (Stewart and Rogoff, 1923; Langecker and Stross, 1925), the doses of insulin were determined for each animal and the criteria of their effectiveness were convulsions or a drop in blood sugar below 50 mg. per 100 c.c.

Since Miller and Riddle (1941) had suggested that insulin stimulates the suprarenal cortex to hypertrophy and produces an excessive output of cortical steroids inhibiting carbohydrate metabolism, the blood sugar was estimated in each case on the day of the animal's death; in no case in any of the three series did the fasting blood sugar before insulin injection show any appreciable change. The weight of both adrenals remained within normal limits in all three series.

The adrenalin content of the left gland in series B (animals killed three days after their last insulin shock) revealed an increase of about 75 per cent. above the average normal value, showing at the same

\* The chemical estimations of adrenalin and blood sugar were done by Dr Kawa, for which I wish to thank him.

time a relatively small standard deviation ( $\pm 16$ ). In the series C and D (rabbits killed fifteen and thirty days after the last insulin shock) the average figure for the adrenalin content of the left suprarenal showed lower values (see Table) than in series B, though still slightly above my own controls as well as those quoted by others (Kiyoszi Syozi, 1936-37), again with an admissible or low standard deviation ( $\pm 22.6$  and  $\pm 6.5$ ). Since the standard deviation of both these averages is in admissible limits, it is obvious that the slightly higher adrenalin content of the left suprarenals in series C and D is not a

TAB I  
*The Data of Avera*

Type of Experiment.	Suprarenals.		Medulla Dimensions in mm.			Medullary Cell Dimensions	
	Weight of both Glands in g.	Adrenalin Content of Left Gland in $\gamma$ .	Longitudinal Axes in mm.	Transverse Axes in mm.	Dorso-ventral Axes in mm.	Of Active Zones (Mean of 50).	Of Inactive Zones (Mean of 50).
SERIES A 12 controls	0.415	138	6.19	1.79	1.31	14.5 $\times$ 9.0	13.4 $\times$ 8.1
s.d.	$\pm 0.639$	$\pm 12$	$\pm 0.25$	$\pm 0.19$	$\pm 0.09$	$\pm 0.35$ ; $\pm 0.20$	$\pm 0.22$ ; $\pm 0.1$
SERIES B 5 rabbits (3 days)	0.410	243	7.63	2.16	1.69	18.5 $\times$ 11.5	18.0 $\times$ 11.1
s.d.	$\pm 0.058$	$\mp 16$	$\mp 0.29$	$\pm 0.15$	$\pm 0.10$	$\pm 0.60$ ; $\pm 0.39$	$\pm 0.58$ ; $\pm 0.5$
SERIES C 5 rabbits (15 days)	0.427	186	7.42	1.87	1.29	19.9 $\times$ 12.5	16.1 $\times$ 10.3
s.d.	$\pm 0.054$	$\pm 22.6$	$\pm 0.44$	$\pm 0.21$	$\pm 0.12$	$\pm 1.13$ ; 0.32	$\pm 1.51$ ; 0.54
SERIES D 5 rabbits (30 days)	0.412	184	7.38	2.00	1.12	20.2 $\times$ 12.7	18.5 $\times$ 11.9
s.d.	$\pm 0.05$	$\pm 6.5$	$\pm 0.27$	$\pm 0.24$	$\pm 0.073$	$\pm 0.37$ ; $\pm 0.23$	$\pm 0.91$ ; $\pm 1.01$

coincidence but a phenomenon repeating itself constantly or almost constantly. The indubitable hyperproduction of adrenalin shown by animals of series B strongly supports the view that these values are true and above the normal level, particularly in view of the persistence of the histological signs of hyperactivity of the medulla.

The shape of the normal medulla is an ellipsoid; there are cases, however, in which the medulla is completely split up, *e.g.* No. 4 of series B; there are also cases in which patches of medullary tissue are scattered through the cortex or present in the connective tissue surrounding the gland, *e.g.* No. 5 of series D; or there may be an entire additional suprarenal gland (Stewart, 1924). Therefore the approximate evaluation of the whole volume of the medulla can be

made only by measuring the maximal longitudinal, transverse and dorso-ventral axes and, if necessary, adding the corresponding figures for additional masses of medullary tissue. Only one of the animals showed such satellite masses, so that the error introduced by this admittedly unsatisfactory correction is not great. The most conspicuous difference between the values of series B, C, D and the controls lies in their longitudinal axes, which showed an increase of about 20 per cent. in the experimental animals over the controls. The average values of other axes do not produce such convincing

*of each Series*

2.	Nuclear Dimensions of Medullary Cells in $\mu$ .			Number of Nuclei per sq. mm.	Number of Mitotic Figures per sq. mm.	Active : Inactive Zones.
	Of Active Zones (Mean of 50).	Of Inactive Zones (Mean of 50).	Mean of Total 200 Nuclei.			
Mean of Total (100).						
13.9×8.5 0.23; ±0.15	7.3×5.6 ±0.13; ±0.11	7.2×5.4 ±0.11; ±0.09	7.3×5.5 ±0.10; ±0.06	72 ±2.4	0.5 ±0.2	1.6 : 1.8 ±0.3; ±0.3
18.2×11.3 0.49; ±0.42	8.6×6.5 ±0.18; ±0.21	8.1×6.1 ±0.20; ±0.2	8.3×6.3 ±0.17; ±0.18	48 ±3.0	1.8 ±1.1	3 : 1 ±0.4; ±0.0
18.0×11.4 1.31; ±0.23	7.4×6.1 ±0.48; ±0.26	6.7×5.5 ±0.29; ±0.16	7.0×5.8 ±0.39; ±0.13	58 ±3.7	0.4 ±0.24	2 : 2 ±0.6; ±0.45
19.3×1.23 0.63; ±0.58	8.2×6.1 ±0.63; ±0.25	6.1×5.1 ±0.44; ±0.22	7.1×5.6 ±0.45; ±0.18	55 ±2	0.6 ±0.24	2.2 : 1.4 ±0.37; ±0.40

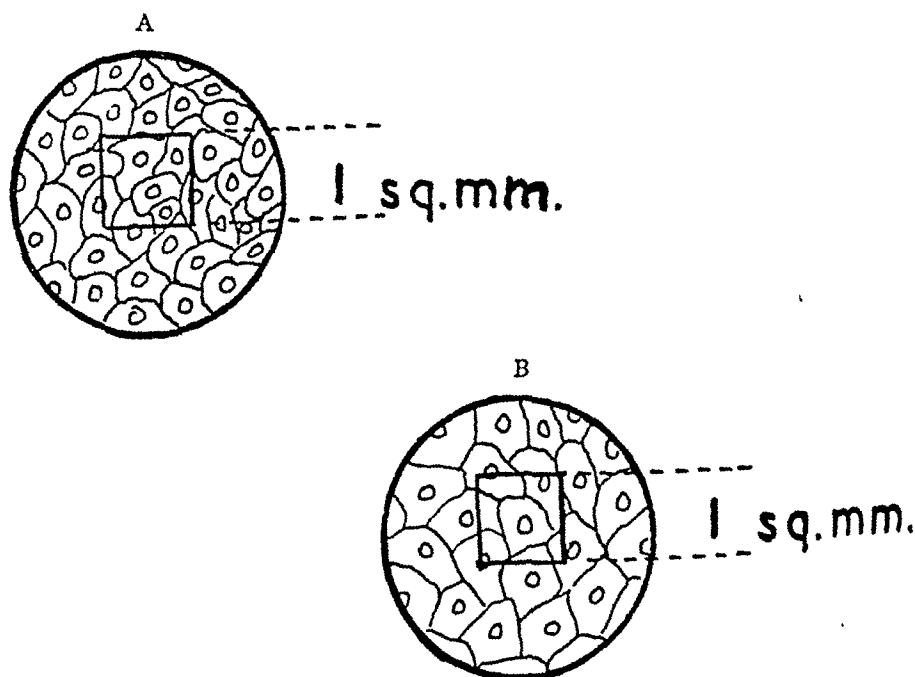
figures, although the photomicrographs (Figs. 1-4) showed an undoubted enlargement of the medulla in all dimensions. There are, however, wide fluctuations in the standard deviation of these averages.

In order to elucidate whether the enlargement of the medulla is due to a simple hypertrophy or hyperplasia, or both, or only to a hyperemia, the measurement of the cells of the medulla as well as of the size of the large and medium blood vessels has been carried out. The average values for the cells in all three experimental series showed a substantial increase in both dimensions, although the standard deviation for certain of these values is high (*e.g.* the cell dimensions in series C and D). Nevertheless even the lowest value of the cell dimensions in these two series is much above the average value of the



controls (the lowest value of series C was  $15.9 \times 12.0 \mu$  and of series D  $17.4 \times 11.1 \mu$ ). The high standard deviation in these series is due to the very high values of the cell dimensions in series C (no. 4,  $23.1 \times 11.8 \mu$ ) and of series D (no. 5,  $21.3 \times 14.4 \mu$ ). Therefore the enlargement of the cell dimensions in all three series has to be accepted as fairly constant. The occurrence of this change simultaneously with the hypertrophy of the whole medulla throughout all three series leads to the conclusion that the hypertrophy of the medulla is due to the hypertrophy of the cytoplasm of the individual cells. The large and medium vessels in all three series were within the normal limits; capillaries, however, were considerably dilated in series B—further proof of the remarkable hyperactivity of the medulla in this series; in series C and D the capillaries were almost within normal limits (Figs. 5-8).

To confirm the fact of hypertrophy of the cytoplasm throughout all three series, the evaluation of the number of nuclei per sq. mm. was undertaken, since the boundaries of the cytoplasm were often not easily distinguishable; the following diagram explains the principle of this evaluation.



A. Unhypertrophied medulla; B. Hypertrophied medulla. Description in text.

These counts indicate fewer nuclei per sq. mm. in series B, C and D than in the control glands, with a low standard deviation, which strongly confirms the presence of hypertrophy in the former.

The average value of the size of nuclei, taken as one of the signs of the hyperactivity, shows a considerable increase, with a relatively low standard deviation in series B simultaneously with other signs of hyperactivity shown in Fig. 6 such as dilatation of intercolumnar



FIG. 1.—Average normal suprarenal medulla of a rabbit.

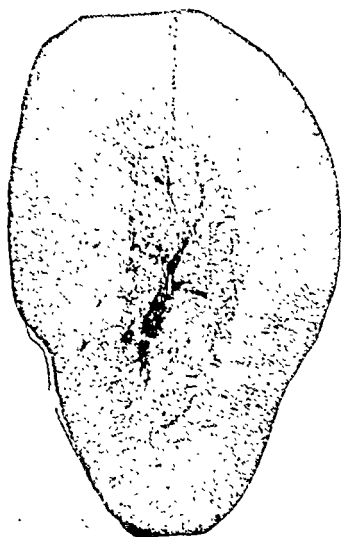


FIG. 2.—Average of five enlarged medullas of rabbits killed 3 days after last i.s.

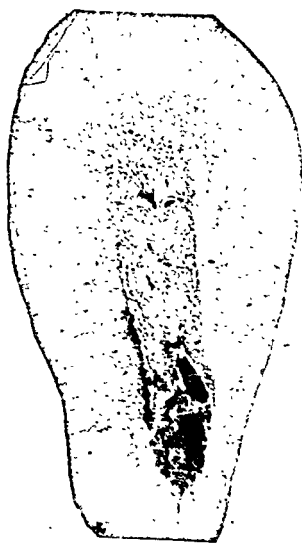


FIG. 3.—Average of five enlarged medullas of rabbits killed 15 days after last i.s.



FIG. 4.—Average of five enlarged medullas of rabbits killed 30 days after last i.s.

Magnification: 11 times.

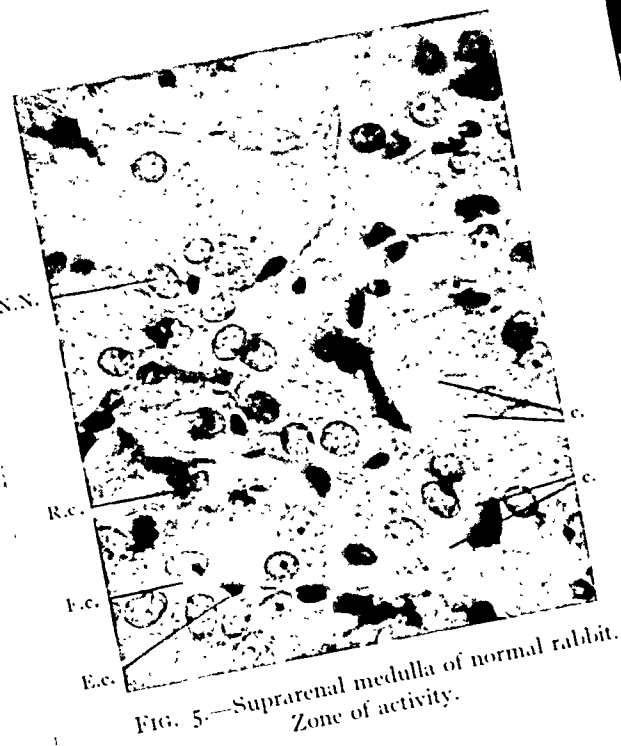


FIG. 5.—Suprarenal medulla of normal rabbit.  
Zone of activity.

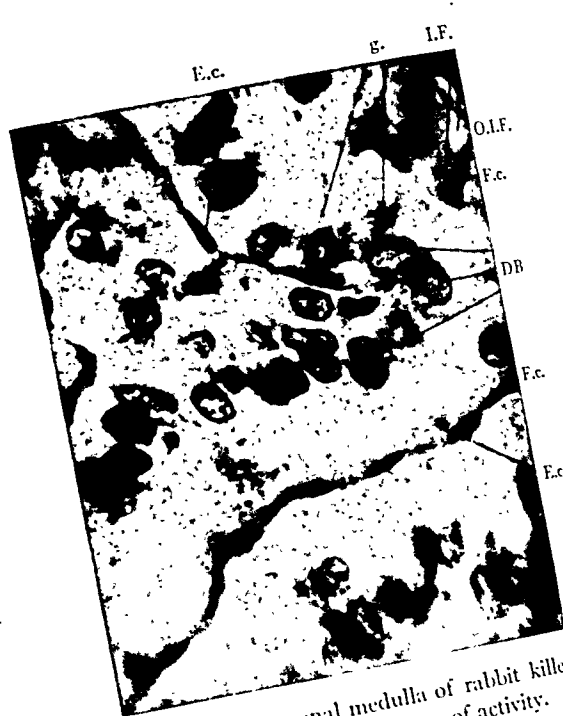


FIG. 6. Suprarenal medulla of rabbit killed  
3 days after last i.s. Zone of activity.

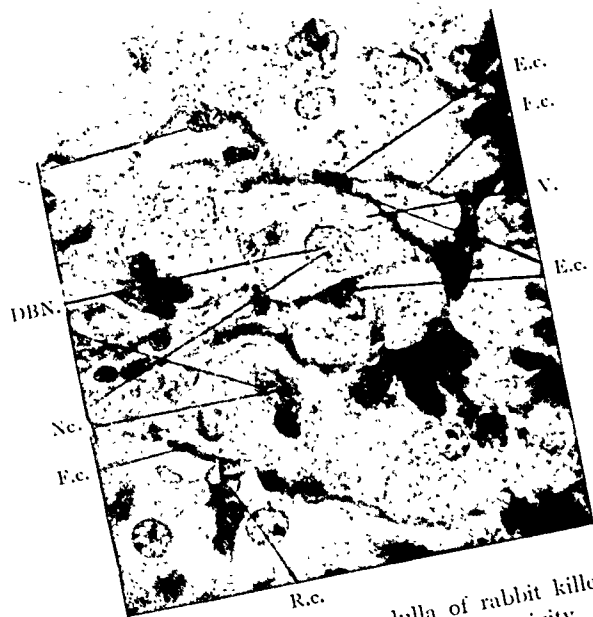


FIG. 7.—Suprarenal medulla of rabbit killed  
15 days after last i.s. Zone of activity.



FIG. 8.—Suprarenal medulla of rabbit killed  
30 days after last i.s. Zone of activity.

Magnification : 1000 times.

c.: cells of medulla. E.c.: Endothelial cells. F.c.: Felicine's canals. DBN.: Dark big nucleus. N.N.: Normal nucleus. I.F.: Intercellular fissure. O.I.F.: Opening of intercellular fissure. g.: granulations. Nc.: Nucleolus. R.c.: Red corpuscles. V.: Vacuoles.

canals (F.c.) and intercellular fissures (I.F.) and their openings (O.I.F.), swelling of endothelial cells (E.c.), granulation of cytoplasm (g.), intensity of nuclear staining (DBN). The nuclei in series C and D (Figs. 7 and 8) are either normal in size or only slightly increased in zones of activity; the other signs of hyperactivity are still present, but to a much less extent than in series B, again proving the diminution in the hyperactivity in these two late series.

The high number of mitotic figures per sq. mm. in series B suggests a higher rate of cellular regeneration, in other words a co-existing hyperplasia in this series.

The ratio of active and inactive zones of the medulla shows an apparent increase of the former in series B, while the ratios in series C and D are similar to that found in the controls.

### DISCUSSION

Should we then consider such a state in which the suprarenal medulla is hypertrophied and its function elevated as a pathological one? The answer to this question is both yes and no. Hypertrophy undoubtedly took place in the present experiments and the function of the medulla was raised considerably in animals killed in early stages after insulin shock and still appreciably, although in much lesser extent, in animals killed in later stages. One must bear in mind, however, that the original aim of the present series of experiments was to find out the mechanism of the therapeutic action of insulin shock in bronchial asthma, *i.e.* in a pathological condition which almost always responds to adrenalin injection by complete but temporary remission of symptoms. To produce in experimental animals a human type of bronchial asthma is difficult, so the experiments must be carried out on normal animals. Therefore the condition produced by repeated insulin shock in normal rabbits is pathological; in human bronchial asthma, where the activity of the sympathetic-medullary system is impaired, such a condition would be highly desirable. Cannon (1930) showed that adrenalin is normally liberated in significant amounts into the circulation only "spasmodically" and in an "emergency" state of the organism, *i.e.* only when secretory impulses are transmitted to the medulla through the splanchnic nerves. The amount of the adrenalin secreted by a hypertrophied medulla when stimulated by a physiological stimulus will probably be higher than that produced in response to the same stimulus by a non-hypertrophied medulla. If, however, a normal or pathological stimulus in an individual suffering from bronchial asthma results in a higher output of adrenalin due to hypertrophy of the medulla, such a response would be at least highly desirable both in the prevention and treatment of the existing pathological state. In such individuals, therefore, any hypertrophy or hyperfunction of the medulla may be regarded not as pathological but as a beneficial return towards normality.

## SUMMARY AND CONCLUSIONS

(1) Toxic doses of insulin causing hypoglycæmic convulsions in rabbits, when repeated ten times, produced hyperactivity of the suprarenal's medulla, giving a higher production of adrenalin; this increased activity slowly declined but did not return to the pre-experimental level, remaining slightly elevated for at least thirty days.

(2) This was associated with hypertrophy of the suprarenal medulla, persisting for the whole experimental period of thirty days; this hypertrophy was due to the hypertrophy of the cytoplasm of the individual cells of both active and inactive zones of the medulla. The morphological signs of the medullary hyperactivity, pronounced in the early stages after the last insulin shock, diminished slowly but did not recede to the normal level of activity at the end of the experimental period. The degree of hypertrophy is not necessarily parallel to the functional activity of the suprarenal medulla.

(3) The parallelism in the biological and histochemical evidence of increased action of the medulla in series C and D as well as in the early stages substantially supports the view that these results are not due to an experimental error.

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## THE ÆTIOLOGY OF ERYTHEMA NODOSUM

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THE relationship between erythema nodosum and rheumatism was first described by Bouillaud in 1840. This view has been generally accepted in this country until recently when Ernberg, in 1932, showed that the eruption known as erythema nodosum was usually followed, after a short interval of a few months, by tuberculosis. Prior to Ernberg's publication, other workers had questioned the theory of rheumatism playing a part in the ætiology of erythema nodosum. Bouillaud's statement that erythema nodosum was a rheumatic disease was based on the frequent occurrence of pains in the limbs associated with the eruption. This suggestion was supported by Trousseau (1869) in his lectures on clinical medicine. In 1883, however, Barlow questioned the opinions of the previous workers and stated that until there was evidence of heart disease following an attack of erythema nodosum there was no basis for any causal relationship between rheumatism and erythema nodosum. Mackenzie, in 1886, supported Bouillaud and Trousseau, and claimed to have shown such a relationship. This view has been generally accepted.

Gosse in 1913 and Symes in 1928 observed that myocarditis was rarely found in cases of erythema nodosum, that erythema nodosum was more frequently present in females, whereas males and females were almost equally affected in rheumatic fever and that salicylates had no effect on the course of the eruption. Despite these criticisms, however, the rheumatic theory of erythema nodosum has continued to be accepted by many clinicians.

In view of the fact that small epidemics of erythema nodosum are sometimes seen, Lendon (1905 and 1925), Symes (1921), Walker (1927) and Keil (1939) suggested that the disease was of the nature of a specific infection. Ernberg in 1932 and Wallgren even earlier, in 1926, showed that erythema nodosum was usually followed by some manifestation of tuberculosis. They demonstrated that children, in whom the incidence of a positive tuberculin reaction was low, with the development of erythema nodosum show a strongly positive tuberculin reaction. In 1939 Arnaud observed that if a tuberculin test is performed when the eruption is fading, not only is the test strongly positive but there is a recrudescence of the erythema. The findings of these workers would suggest that the ætiology of erythema nodosum is connected in some way with an infection by the tubercle bacillus.

Interest was taken in this subject when, about a year ago, a young

woman, aged twenty-four years, was seen at the out-patient department, suffering from erythema nodosum. She stated that her infant son, aged nine months, had just died of tuberculous meningitis. An X-ray of her chest revealed a primary tuberculous infection. The patient is now in a sanatorium suffering from active pulmonary tuberculosis.

Cases of erythema nodosum admitted to General Medical Ward have been examined to see if any light could be thrown on the matter.

### ANALYSIS OF CASE MATERIAL

Twenty patients suffering from erythema nodosum were admitted from 1928 to 1946, a surprisingly small number.

*Sex and Age.*—Eighteen of the cases were females and 2 were males, these latter cases being boys aged eight and fourteen years. Below the age of fifteen years there were 5 girls and 2 boys, while over the age of fifteen years there were 13 females and no males. The average age of the patients in this series was 21·6 years, the average age for the males eleven years and for the females 22·5 years. These figures support the observations of Perry who showed that in his series there were 80 boys and 31 girls under fifteen years of age, whereas over this age there were 45 females and only 2 males. Hence erythema nodosum would appear to be more common in females than in males. This would suggest that some endocrine factor plays a part in the predisposition to the disease.

*Duration.*—Twelve of the cases had complained of the eruption for fourteen days prior to seeking admission to hospital, 4 cases had had erythema nodosum for a week and 2 for two days, 1 for three weeks and 1 for five months before admission to hospital. The majority of the patients had had the eruption for fourteen days and the eruption disappeared in approximately one week after admission. The total duration of the erythema nodosum in the majority of cases was about three weeks.

*Immediate Preceding Illness.*—Seven of the patients gave no history of any illness before the onset of the eruption, while tonsillitis and pharyngitis preceded the disease in 8 cases, arthritis in 4 cases. Both tonsillitis and arthritis occurred together in 2 of the patients mentioned above, and the eruption appeared during an attack of lobar pneumonia in one case.

*Previous Health.*—Four of the patients gave a history of repeated attacks of tonsillitis, 2 others had suffered from growing pains, another from rheumatic fever and one from tuberculous glands of the neck. The remaining 12 patients gave no history of any significant disease.

The preceding illnesses and the previous health of the patients in this series might suggest an ætiological association with rheumatism.

*Family History.*—In only 3 cases was there a family history of tuberculosis. This figure must be taken with reserve, however, for no account is taken of possible contact with unknown cases of tuberculosis.

*Cardiac Lesions.*—There was no clinical evidence of cardiac enlargement in any of the cases. Six patients had a soft apical systolic murmur which was not propagated and disappeared after several days' rest in bed. A low-grade pyrexia was present in all the above cases, and it was thought that the systolic murmur was probably febrile in origin. A control group of 20 other young patients were examined and an apical systolic murmur was present in 4 of them. The presence of the apical systolic murmur in the patients suffering from erythema nodosum is probably not significant. Electrocardiograms were taken in 12 of the 20 patients and no abnormality was detected in any of them.

*Radiological Examination of the Chest.*—Four patients in this series had no X-ray examination of the chest. No abnormality was detected in 10 cases, and in all of the remaining 6 cases the X-ray revealed prominent hilar shadows, glandular enlargement and increased broncho-vascular markings in the peri-hilar areas. Infiltration of the lung substance in the zones corresponding to the glandular enlargement also occurred in 2 of these cases. This latter appearance was interpreted as a primary tuberculous infection. Of the 16 cases X-rayed, 6 showed changes in the lungs. It is interesting to compare these figures with those of Kerely. He X-rayed 37 patients who were suffering from erythema nodosum and found abnormalities in the lungs in 28 of them. These changes were of two types, glandular enlargement, usually bilateral and a coarse reticular striation in the lungs, very like the picture of early silicosis. This latter appearance, however, may be due to variations in the penetration of the X-rays. This observer suggested that the pulmonary shadows were very like the changes seen in sarcoidosis, and in 2 of his cases skin biopsies showed a histological picture in keeping with this diagnosis. Four cases in his series showed the presence of calcified hilar glands, thus demonstrating that the primary tuberculous infection had occurred years before and hence could not be related to the erythema nodosum.

*Tuberculin Tests.*—A mantoux test was performed on 16 of the 20 patients in this series. The dose used was 0.1 c.c. of 1 : 1000 Koch's old tuberculin. In 5 of the cases the test was negative; it was positive in 6, and strongly positive in 5 of the patients. In a control group of 16 persons of similar ages all gave a positive mantoux test, but in none of them was it strongly positive. It is interesting to compare these findings with the X-ray appearances, and sex and age (see Table). In every case showing changes in the lungs the mantoux test was positive and in the 2 cases with a primary tuberculous infection the test was strongly positive.

*Throat Swab.*—The throat was examined bacteriologically in 15 of the 20 patients. Hæmolytic streptococci were present in 4 of the cases, in whom the eruption had been preceded by acute tonsillitis. Collis in 1932, and Coburn and Moore in 1936, have shown skin sensitivity of patients to streptococcal nucleoprotein at the time of



the eruption and exacerbation of the disease, following the intracutaneous injection of nucleoprotein of hæmolytic streptococci. In their cases, however, the tuberculin test was negative, while it was positive in the 4 patients in this series.

*Follow-up Examination.*—Of the 20 patients examined originally only 11 could be traced for re-examination, the result no doubt of the shifting population. All these patients were submitted to a tuberculin test, and X-ray examination of the chest and an examination of the heart. In none of the cases was any cardiac lesion detected. Four of the cases had developed definite evidence of pulmonary tuberculosis and were undergoing treatment for this condition. The accompanying table shows the mantoux reactions and X-ray examinations in the

TABLE

Sex.	Original Examination.			Follow-up Examination.		
	Age.	Tuberculin Test.	X-Ray.	Age.	Tuberculin Test.	X-ray.
Male	8	—	—	0	0	0
Female	10	—	—	17	+	—
Female	12	—	—	15	+	—
Male	14	—	—	18	+	—
Female	14	—	—	21	+	—
Female	14	+++	+	20	+	—
Female	14	+++	+	17	+	T.B.
Female	14	0	0	0	0	0
Female	15	+	+	19	+	—
Female	15	+++	++	17	+	T.B.
Female	17	+++	+	18	+	T.B.
Female	22	0	—	30	+	—
Female	23	0	—	0	0	0
Female	24	+++	++	25	+	T.B.
Female	25	+	—	0	0	0
Female	28	0	0	0	0	0
Female	33	+	—	0	0	0
Female	34	+	0	0	0	0
Female	37	+	—	0	0	0
Female	58	+	0	0	0	0

follow-up series compared with these findings obtained at the original examination. Of the 4 cases with established pulmonary tuberculosis, 2 had evidence of a primary infection at the first examination at the time of the eruption. The other 2 had a strongly positive mantoux test, hilar glandular enlargement and increased peri-hilar broncho-vascular markings on radiological examination, when admitted originally for the erythema nodosum. All 5 cases with strongly positive tuberculin tests, at the time of the eruption, showed radiological changes in the lungs.

These findings would suggest that cases of erythema nodosum, having a strongly positive tuberculin test and showing X-ray changes in the lungs, will be prone to develop tuberculosis. The other cases, with no radiological abnormalities or with a normally positive tuberculin test, would appear to develop erythema nodosum in association with some other disease, possibly rheumatism.

## SUMMARY

1. Twenty cases of erythema nodosum are reviewed.
2. Seven patients gave no previous history of rheumatism or other significant disease, while 12 suffered from tonsillitis or arthritis prior to the onset of the eruption.
3. Four patients showed X-ray changes in the lungs and strongly positive tuberculin tests. Two of these were found to have tuberculosis at the original examination and the remaining 2 developed tuberculosis at a later date.

I wish to thank Professor Murray Lyon for the use of the case material and for his advice and help in the compilation of this paper.

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## VITAMIN A CONTENT IN HUMAN LIVER

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and the Polish School of Medicine, Edinburgh*

THE importance of the liver in vitamin A metabolism is well recognised as it is the place of conversion of carotene into vitamin A and the storehouse of this vitamin. According to Moore, 95 per cent. of the total vitamin A of the body is stored in the liver.

It has been found that pathological changes in the liver may produce symptoms of vitamin A deficiency. Patek and Haig reported hemeralopia in cases of liver cirrhosis even without jaundice. Night-blindness has been also reported by Wohl and Feldman in acute hepatitis.

In previous publications we have given the results of our investigations into the vitamin A excretion in urine and the vitamin A concentration of blood and body fluids in health and disease. We have found particularly low vitamin A value in blood in cases of liver disease, especially infective hepatitis and cirrhosis, confirming the findings of Haig and Patek, Popper *et al.*, Lasch and others.

During our investigations of vitamin A in human subjects in health and disease we sometimes encountered very marked discrepancies between the vitamin A concentration in the blood and in the liver. To understand this problem better we carried out a series of determinations of liver vitamin A on post-mortem cases. In some of the cases determination of blood vitamin A was also made. We wanted to examine the possible correlation of certain diseases with vitamin A reserves in the liver. By comparing the results with the pre-war values reported for this country, we could get also an idea of the vitamin A reserves in the Scottish people after five years of war-time food restrictions.

The investigations were made on the material from the Pathological Department of the Royal Infirmary of Edinburgh, for which we are indebted to Professor M. Drennan.

### METHOD

A modification of Davies' (1933) method was used for the extraction of vitamin A and carotene from the liver. Five gm. of the liver tissue, cut in small pieces, were placed in 10 c.c. of 3 per cent. potassium hydroxide in a 50 c.c. conical flask. In order to dissolve the liver tissue the mixture was heated in a boiling water bath for about twenty to thirty minutes. The digest after cooling was transferred to a funnel, an equal volume of absolute alcohol was added and the mixture was shaken for a minute. Forty c.c. of ether were then added and the

mixture was shaken for five minutes. The ether layer was removed and another extraction with 40 c.c. of ether was made. From the combined extracts ether was distilled off and the residue dissolved in 50 c.c. of petroleum ether, grade 40-60. The petroleum ether solution was washed once with 25 c.c. 3 per cent. KOH and twice with 50 c.c. of distilled water. After drying over anhydrous sodium sulphate for some time the petroleum ether was distilled down to about 5 c.c. This was transferred to a graduated flask and made up to 10 c.c. with petroleum ether. Carotene was estimated at this stage according to the method of Działoszyński, Mystkowski and Stewart (1945). After the estimation of carotene, petroleum ether was distilled off completely and the remaining residue dissolved in 10 c.c. of dry chloroform.

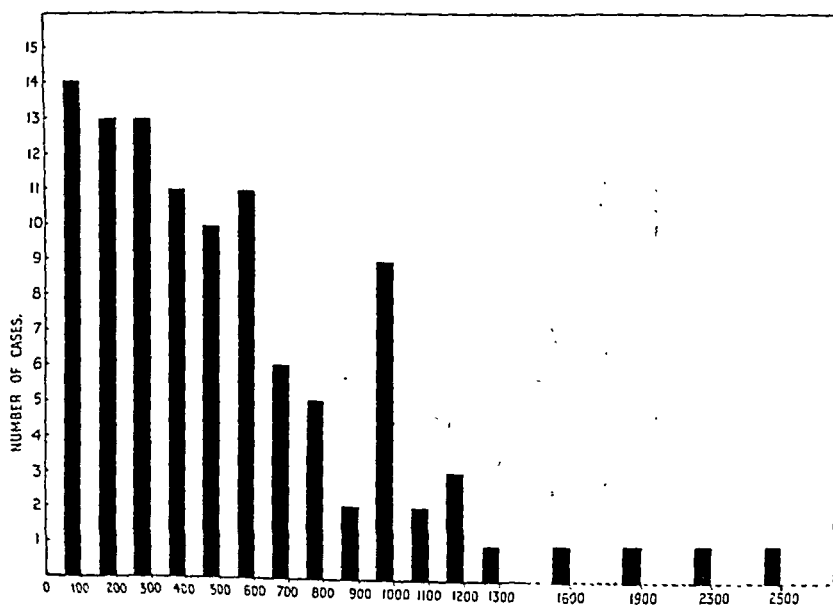


FIG. 1.—I.U. of Vitamin A.

0.5 c.c. of this solution was made up to 5 c.c. with chloroform and the vitamin A estimated by Spekker photo-electric colorimeter. In the case of livers containing very great amounts of vitamin A an appropriate dilution with chloroform had to be made. The transfer of the extracts from ethyl ether to petroleum ether was done in order to estimate carotene in the same solvent as was used for the preparation of the calibration curve, *i.e.*, petroleum ether. Vitamin A was expressed in international units (I.U.) and carotene in micrograms per gram of wet liver.

## RESULTS

Altogether 103 livers were examined. The investigations were made mostly during the winter and spring of 1945. The age of the subjects varied from twelve to eighty years.

*Range of Distribution.*—In the first place we were interested in the range of distribution of carotene and vitamin A in the livers of all the subjects. This could serve more or less as an index of the average vitamin A content in the liver of the people of South-East Scotland.

The results are given in Fig. 1, which shows the distribution of liver vitamin A values. It is evident that the great majority of cases (70 per cent.) are closely grouped in the range of 0-600 I.U. and 30 per cent. are above 600 I.U., showing a much greater range of distribution from 600-2400 I.U.

The average value of vitamin A in the liver of 103 cases was 504 I.U., the median being 406 I.U. There are single cases showing unusually high vitamin A values up to nearly five times the average value.

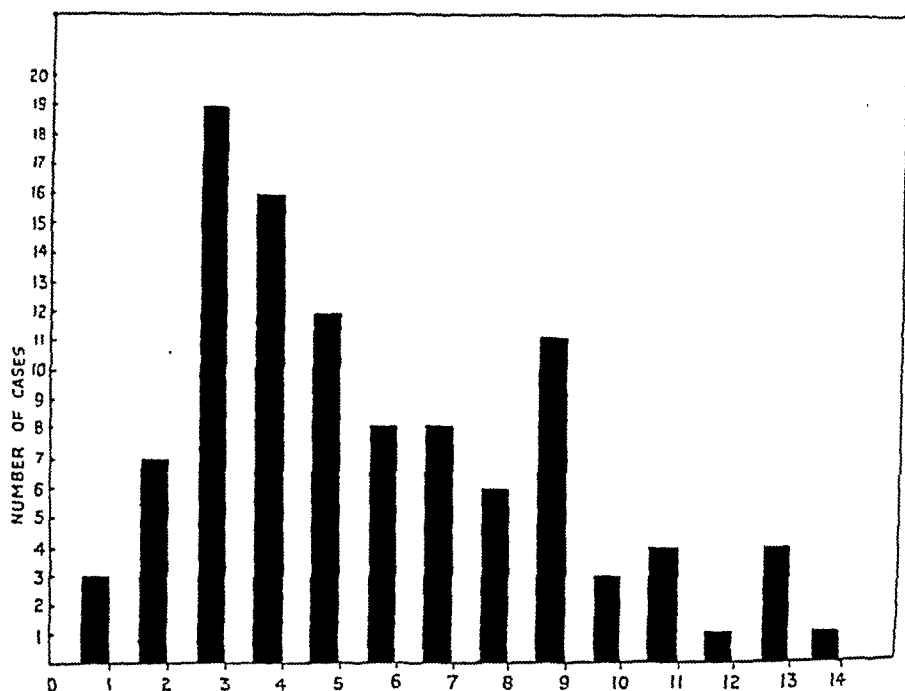


FIG. 2.—Microgram of  $\beta$ -carotene.

Fig. 2 shows the distribution of carotene in the liver in 103 cases. The average value for all the cases is 5.4 mg., the median being 4.4 mg. The range of distribution is not so great as in vitamin A values.

*Vitamin A and Age Groups.*—As the average value of all the cases gives us only a rough idea of the vitamin A concentration in livers of the population, we tried to find out whether there is any correlation to age. We divided the whole material into age groups by decades. The results are given in Table I.

As the table shows, there are rather lower values in the younger age groups. The range of distribution is also narrower. There is a much wider range of distribution of vitamin A in the higher age groups, and the unusually high values were found rather in the older people. The number of cases in the younger age group is too few to form any definite conclusion.

*Vitamin A in Relation to Disease.*—The post-mortem material has been divided into groups in which some disturbance of vitamin A could be expected, and these have been compared with a group of subjects who had died suddenly from street accidents or internal catastrophes, free from protracted or emaciating diseases.

1. Street and internal accidents, sudden death, cerebral hæmorrhage, death after operation in sudden surgical illness.

TABLE I  
*Vitamin A Values in Relation to Age.*  
*The Numbers Represent I.U. in 1 Gram of Wet Liver*

Age.	Number of Cases.	Vitamin A in I.U.			
		Minimum.	Maximum.	Average.	Median.
11-20 . . . .	12	1	1038	306	206
21-30 . . . .	7	10	978	452	502
31-40 . . . .	13	67	897	360	283
41-50 . . . .	20	56	2453	555	322
51-60 . . . .	22	20	1125	528	511
61-70 . . . .	21	26	1860	558	455
71-80 . . . .	8	110	2270	657	478

TABLE II  
*Vitamin A and Carotene Values in Relation to Disease*

Diagnosis.	Number of Cases.	Carotene in Micrograms.			Vitamin A in I.U.			
		Minimum.	Maximum.	Average.	Minimum.	Maximum.	Average.	Median.
Street and internal accidents . .	11	2.3	13.4	6.6	67	1860	586	638
Acute infections . .	34	1.8	13.0	5.7	56	2453	603	473
Tumours . . . .	26	0.8	13.4	5.4	47	1518	545	472
Liver diseases . .	7	2.6	10.4	5.6	116	838	414	376
Kidney diseases . .	6	2.8	8.8	5.3	19	607	380	430
Congenital heart failure . . . .	8	1.0	7.6	4.6	1	978	345	261
Chronic infections . .	7	1.0	9.4	4.1	10	677	304	223
Alimentary canal diseases . .	4	1.0	9.4	4.0	26	455	208	177

*Note.*—The average of vitamin A of all the cases is 504 I.U. and the median 604 I.U.

2. Acute infections, pneumonia, bronchopneumonia, meningitis, septicæmia, peritonitis, lung abscess.
3. Neoplastic diseases of all kinds, some with metastases of the liver.
4. Liver diseases, cirrhosis, yellow atrophy.
5. Chronic kidney diseases, chronic nephritis, nephrosis.
6. Congestive heart failure.
7. Chronic infections, tuberculosis, arthritis.
8. Chronic alimentary tract diseases, steatorrhea, chronic ulcerative colitis, œsophageal stricture, chronic intestinal obstruction.

The vitamin A and carotene values in various disease groups are given in Table II.

The "normal" (accidents) group shows a little higher vitamin A value (average 568 I.U.) than the average value of all the cases which is 504 I.U. A somewhat higher value of vitamin A than the total average was obtained in acute infections (average 603 I.U.). In neoplastic diseases the values are about "normal" (average 545 I.U.). A more or less normal value could be expected in acute infections as the progress of these diseases is usually rapid. The results are somewhat surprising in the neoplastic diseases.

Lower values than total average of vitamin A were obtained in liver diseases (average 414 I.U.), in kidney diseases (average 380 I.U.) and in chronic infections (average 309 I.U.). The lowest average value (208 I.U.) was found in chronic diseases of the alimentary canal.

The carotene values had no definite correlation to disease groups.

Any conclusion drawn from Tables I and II has only a limited value as the number of cases in different groups was too small and the variation too great.

## DISCUSSION

Our aims in the present investigation were :—

1. A determination of the vitamin A reserves of the inhabitants of South-East Scotland after five years of food restrictions during the war.

2. An investigation of the relationship between vitamin A body reserves and disease.

We found that the average value of vitamin A for all the cases was 504 I.U. and of carotene 5.4 mg. with, however, the wide range of 1 I.U. to 2453 I.U., the majority of the results being grouped closely in the range from 0.600 I.U. The highest number of cases fell into the range 0.300 I.U. We have found some very low values near to complete depletion of vitamin A in the liver. In Moore's (1937) series there were cases in which the liver reserves were practically nil.

It is difficult to speak about a "normal" reserve of vitamin A in the liver owing to the great variation in the vitamin A values of ordinary persons. The values varied in that group from 67-1860 I.U. One cannot exclude even in the "accident" group an undernutrition or some disturbance in vitamin A metabolism.

The question arises now what values can be considered as subnormal and what is the percentage of such cases. The lowest average vitamin A value in the disease groups is the alimentary canal group (208 I.U.) connected with definite disturbances of absorption. We propose to consider values lower than this as being subnormal. On this basis 25 per cent. of our cases were subnormal, including some of the "normal" group.

Wolff (1932), examining 915 livers in the Dutch population, found that 16 per cent. of the population had subnormal vitamin A reserves. He points out that in the case of chronic diseases this

proportion amounted to 24.2 per cent. This finding could be also confirmed in our material.

Knowing the average vitamin A content in 1 gm. of liver (504 I.U.) the approximate amount of vitamin A in the liver can be calculated. Taking the average weight of the liver as 1500 gms., the total average amount in the liver in the Scottish population would be about 750,000 I.U. With daily requirements of 4000 I.U., this reserve would suffice theoretically for six months. With the highest value of 2453 I.U., the total vitamin A reserve in the liver amounted to about 3,600,000 I.U.

In respect to the age groups, as already mentioned, rather lower values were found in the younger group, but the number of cases in this group was too small to draw any definite conclusion. It is of interest to notice that in the newborn low values were found by Wolff as well as by Ellison and Moore and by others. Wolff found in full-term infants a mean liver reserve of 44 I.U. and in premature infants 41 I.U. In children aged 0-4 weeks Ellison and Moore found a mean vitamin A reserve of 27 I.U.; at ages of 5 weeks to 3 months a mean value 37 I.U.; and from 4-8 months of 130 I.U.

It is of interest to compare our results with the pre-war reserves of vitamin A in livers of the British population. An extensive investigation was made by Moore, who published in 1932 the preliminary reports, and later, in 1937, the results of vitamin A examination of over 900 livers. He found the average value of all the livers to be 220 I.U. It is of interest to notice that the reserves of the American population were higher (Ralli *et al.*, 1941; Haig and Patek, 1942).

It is evident that our average value (547 I.U.) is over 100 per cent. higher than Moore's values. This is a surprising result. The better reserves in livers during war-time are explained probably by a greater consumption of vegetables and possibly of vitamin A preparations by the general public. The fact of undoubted improvement of vitamin A reserves after five years of war is a credit to the British Ministry of Food. One must emphasise, however, that a substantial percentage of people have subnormal vitamin A values, and the higher average value is partly due to a number of persons with particularly high vitamin A reserves.

As regards the correlation between vitamin A reserves and certain pathological states, great variation of values has been found in each disease group. We have found somewhat lower values in liver and kidney diseases, congestive heart failures, chronic infections and, most markedly, in diseases of the alimentary tract.

Theoretically, lower vitamin A reserves could be expected (on normal vitamin A intake) where a disease is impairing absorption, increasing utilisation, decreasing storage ability of the liver, hindering the conversion of carotene into vitamin A and causing the excretion of a substantial amount of vitamin A by the kidney.

In some pathological states values higher than "normal" have been found by various authors. Moore reported values three times



higher in diabetes, due probably to higher intake of green vegetables of slower utilisation. Similar results have been also reported by Wolff. High values have also been found by Moore in exophthalmic goitre.

Subnormal reserves have been reported by Moore in organic heart diseases, non-tuberculous respiratory diseases, septicæmia and certain septic conditions. He points out that in some of these diseases the vitamin A subnormality was probably a secondary effect and not a predisposing factor. Low values for vitamin A have been found by Wolff in pregnancy, whooping cough, syphilis III and IV, chronic nephritis and enteric fever.

It would be interesting to review our lowest and highest values in relation to diseases. The lowest values were obtained in a 16-year-old girl with organic heart disease (1 I.U.), in a 27-year-old man with subacute bacterial endocarditis (10 I.U.), in a 17-year-old girl with chronic nephritis and uremia (19 I.U.), and in a 53-year-old man with carcinoma of the colon with metastases in the liver (20 I.U.).

The highest values were found in a case of a 49-year-old woman with bronchopneumonia (2453 I.U.), in a 77-year-old man with pyelitis and cystitis (2270 I.U.), and in a 63-year-old man with myocardial infarction (1860 I.U.).

It has been shown that after intake of high doses of vitamin A only a small percentage is stored in the body (6 per cent. according to Ellison and Moore). Similar reports have been published by Green. In rats only about 15 per cent. of vitamin A intake is usually stored in the liver (Davies and Moore). In one of our cases (a lymphosarcoma) who had received in five weeks over 4 million I.U. of vitamin A, mostly in intramuscular injections, we found the total amount of vitamin A in the liver to be about 2,800,000 I.U. The vitamin A content in 1 gm. of liver was 1518 I.U.

It must be added that our patients with low vitamin A values had no signs of vitamin A deficiency in the skin and there were no hints in the case records of other gross signs of vitamin A deficiency. However, without the dark adaptation test one cannot safely rule out night-blindness, the earliest and most sensitive clinical sign of vitamin A deficiency.

### SUMMARY

Investigations were made on 103 post-mortem cases to find out the liver content of vitamin A.

A wide variation of vitamin A values in liver was found ranging from practically none to 2453 I.U. per gram of wet liver. The majority of values (70 per cent.) were grouped closely between 0-600 I.U. The average of all the cases was 504 I.U. for vitamin A and 5.4 mgs. for carotene. The highest extremes of vitamin A reserves were met in older people.

Great variation of vitamin A reserves have been found in "normal" people, the average being 547 I.U.

We have found an average vitamin A content of human liver over 100 per cent. higher than pre-war findings (Moore, *loc. cit.*), although a substantial percentage of cases had subnormal amounts.

In respect to disease groups, average low vitamin A reserves have been found in liver diseases, kidney diseases, congestive heart failures, chronic infections and chronic alimentary canal diseases. There was, however, a great variation in each disease group.

We wish to express our thanks to Dr C. P. Stewart for his advice and technical help, and to Professor G. F. Marrian we are grateful for the hospitality in the Biochemistry Department of Edinburgh University.

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## NOTES

A QUARTERLY Meeting of the College was held on 6th May, the President, Dr D. Murray Lyon, in the chair. Dr William Alexander Liston (Edinburgh) was introduced and took his seat as a Fellow of the College.

**Royal College of Physicians of Edinburgh** Drs Philip Maxwell Wood (Halifax, Yorks), Roland Antony Bennett (London), Thomas Elliot Elliot (Edinburgh), Charles Landale Grant (Chislehurst, Kent), James Dunsinor Allan (Bothwell), George Marcus Greig (Watford, Herts), Thomas Ferguson Rodger (Glasgow), Harold Scarborough (Edinburgh), and Robert William Craig, O.B.E., were elected Fellows of the College.

Drs Henry Edmund Seiler (Edinburgh), Jacobus Siebert (Cape Town), (Miss) Scott Lawson Forrest (West Calder, Midlothian), Nicholas Alfred Rossiter (Ermelo, Transvaal), Duncan Alderson Duthie (Bowes, Co. Durham), William Agnew MacFadyen (Cleveleys, Lancs), Hugh Alistair Reid (Liverpool), David Crombie Ross (Kingskettle, Fife), Chalmers Hunter Davidson (Falkirk), Charles George Robertson (Edinburgh), John Malfroy Staveley (Palmerston North, N.Z.), Alan George Seymour Hill, M.C. (Edinburgh), Ivor Ralph Campbell Batchelor (Edinburgh), Abdul Jabbar Abdul Fattah Al Amari (London), Hugh Norwood Robson (Langholm), Bangshi Bilas Mukherji (London), were elected Members of the College.

At a meeting of the Royal College of Surgeons of Edinburgh, held on 15th May, Mr James M. Graham, President, in the Chair, the following who passed the requisite examinations were admitted Fellows: Abdel Hamid Ahmed El Baghdadi, M.R.C.S. ENG., L.R.C.P. LOND. 1940; William Edward Bruce Boscence, M.B., B.S. UNIV. ADELAIDE 1937; Godfrey Phillips Charlewood, M.B., CH.B. UNIV. CAPE TOWN 1932; George Richard Clarke, M.B., CH.B. UNIV. BIRM. 1933; Norah Helen Colquhoun Clarke, M.B., B.S. UNIV. LOND. 1937; Alexander Dalrymple Cuthbert, M.B., CH.B. UNIV. GLASG. 1936; George Degnan, M.D., C.M. UNIV. MCGILL, CANADA, 1939; Allan Campbell Duncan, M.D. UNIV. MANITOBA 1931, L.M.C. CANADA 1931; Johan Gustav Aspelung Du Toit, M.B., CH.B. UNIV. CAPE TOWN 1940; Ahmed Talaat El-Mansuri, M.B., CH.B. UNIV. CAIRO 1941; Harvey Charles Fishman, M.D. UNIV. MANITOBA 1937; Thomas Gregor Fyshe, M.D., C.M. UNIV. MCGILL, CANADA, 1936; Frank Gordon Hollands, M.R.C.S. ENG., L.R.C.P. LOND. 1936; Meyer John Lange, M.R.C.S. ENG., L.R.C.P. LOND. 1935; John Edward Leddy, M.D., C.M. UNIV. MCGILL, CANADA, 1937; John Taylor MacDougall, M.D., C.M. UNIV. MCGILL, CANADA, 1937; Allan Bell McLean, M.B., B.S. UNIV. MELB. 1933; Ernest Bertram Zeller Masterman, M.R.C.S. ENG., L.R.C.P. LOND. 1934; Bindra Ban Ohri, M.B., B.S. UNIV. PUNJAB 1931; Donald Robertson, M.B., CH.B. UNIV. EDIN. 1928; John Cornelius Blair Sergeant, M.B., CH.B. UNIV. EDIN. 1939; Tulsidas Prabhudas Shah, M.B., B.S. UNIV. BOMBAY 1940; Leslie Gordon Percival Shiers, M.R.C.S. ENG., L.R.C.P. LOND. 1938; Samuel Skapinker, M.B., B.CH. UNIV. WITWATERSRAND 1940; Cyril South, M.B., CH.B. UNIV. SHEFFIELD 1936; Ronald Yates Stevenson, M.B.,

B.S. UNIV. LOND. 1937; Archibald Mathison Stewart, M.B., CH.B. UNIV. EDIN. 1940; Dattatraya Vishnu Virkar, M.B., B.S. UNIV. BOMBAY 1939; Sydney Wassyng, M.B., B.CH. UNIV. WITWATERSRAND 1939; Benjamin Weston Wells, M.R.C.S. ENG., L.R.C.P. LOND. 1940; Thomas Edward Wilson, M.D. UNIV. MELB. 1939; Benjamin Winter, M.D. UNIV. TORONTO 1941; James Wishart, M.B., CH.B. UNIV. GLASG. 1938; Gordon Neville Wright, M.B., B.S. UNIV. LOND. 1936; Robert Brash Wright, M.B., CH.B. UNIV. GLASG. 1937.

Royal College of Physicians of Edinburgh	LIST of Candidates who have passed their examinations and have become Licentiates of the three Royal Scottish Corporations on 12th April 1947. Michael Shuttleworth Barnett, Harry Yuille Caldwell, Reuben Hyman Freedman, John McDiarmuid Hanley, William Pearse Hanley, Garnet McDermott, Josephine Bernadette McElroy, Hugh McIntyre, Reuben David Watssman, Ephraim Frank Weiswasser, Alexander MacDonald Westwater, N. G. Philip de Silva Wijesekera, Mariella Murray Williams.
Royal College of Surgeons of Edinburgh	
Royal Faculty of Physicians and Surgeons of Glasgow	

## NEW BOOKS

*Modern Management in Clinical Medicine.* By F. KENNETH ALBRECHT, M.D. Pp. ix+1238, with 237 illustrations, many in colour. London: Baillière, Tindall & Cox. 1946. Price 55s.

This is a unique type of book not fully described by its title. The author says it is intended for the consulting room, not the library. His purpose is to present a clear picture of the rationale of therapy, together with useful and usable information in detail about the technique of therapy. Methods of treatment are fully given in rather dogmatic yet frankly critical fashion, but the book contains a good deal more than an account of therapeutic measures. Etiology, signs and symptoms are clearly recorded, often in tabular form. Differential diagnosis is particularly well presented but the author has little to say of prognosis. There are special sections of tropical disorders, skin diseases and geriatrics, and a great deal of attention has been given to clinical laboratory methods.

This excellent book should prove of the greatest value to the practitioner who is interested in modern methods.

*Ophthalmic Optics as a Career.* By F. R. CORNWELL. Pp. 68, with 11 figures. London: Vawser & Wiles Ltd. 1946. Price 5s. net.

The author gives an account of his subject and its development and describes the eye and its functions. He then discusses several aspects of the optician's work, status and training. The book is well written and attractively produced.

*Circulation in the Fetus.* By K. J. FRANKLIN, D.M., F.R.C.P., A. E. BARCLAY, D.M., F.R.C.P., and M. L. PRICHARD, M.A. Pp. iv+28, with 13 figures. Oxford: Blackwell Scientific Publications. 1946. Price 2s. 6d. net.

This paper-backed pamphlet gives a short survey of the material incorporated in a larger text-book produced by the authors two years ago. Its object is to make the specialised information available to students and others who have not the time to study the larger book. The authors summarise earlier work on the subject, then give a survey of present knowledge and suggest future lines of investigation. An excellent series of illustrations is included.

*Handbook of the Scientific Instrument Manufacturers' Association of Great Britain Ltd.* 123 Pall Mall, London, S.W. 1.

Among other objects the Manufacturers' Association exists to encourage co-operation, discourage overlapping in production and promote research. The present booklet has evidently been produced for the convenience of those in charge of laboratories, to enable them to find where various pieces of apparatus can be obtained. It includes a long classified list of scientific instruments and by an ingenious arrangement refers the reader to the appropriate page in the advertisement section which occupies a large part of the book.

*William Beaumont's Formative Years.* Edited by GENEVIEVE MILLER, M.A. Pp. xv+87, with 19 illustrations and a map. New York: Henry Schuman 1946. Price \$6.

Miss Miller has given us the contents of two manuscript notebooks written by Beaumont in his early years. The story begins when Beaumont was an apprentice with Dr Chandler, a disciple of the Brunonian system. He gives a description of some of the more striking cases he came across. Then he served with the military forces campaigning in the neighbourhood. After this he practised for five years at Plattsburg, and gave this up to rejoin the arm on the frontier. The period extends from 1811 to 1821. The first notebook includes excerpts from medical books, various prescriptions and notes of his military service; the second extracts from his general reading and an account of his travels. They have been reproduced exactly as written, and Miss Miller has added copious and helpful notes to explain obscure passages. The book has been very artistically produced and is a valuable contribution to the history of medicine.

*Practical Anaesthetics.* By H. PARRY-PRICE, M.R.C.S., L.R.C.P., D.A. (R.C.S.). Pp. iv +127, with 50 illustrations. Bristol: John Wright & Sons Ltd. 1946. Price 12s. 6d. net.

This little book is essentially a record of personal experience and as such has a somewhat limited value. It is certainly not the book for the student who wishes to learn about anaesthesia, but for the practising anaesthetist it has some points of interest and of practical value. The English, about which there is a nautical breeziness, is not above criticism, and the format might be improved, as for example where the table indicating the stages of anaesthesia finds itself out of relationship to the text. The general production of this booklet, including the illustrations, is good.

*Physics for the Anaesthetist.* By R. R. MACINTOSH, M.A., M.D., F.R.C.S., D.A., and W. W. MUSHIN, M.A., M.B., B.S., D.A. Pp. v+235, with 282 illustrations. Oxford: Blackwell Scientific Publications Ltd. 1946. Price 30s.

This latest book from the Nuffield Department of Anaesthetics of the University of Oxford illustrates the comprehensive scale of investigation of anaesthetic problems possible in this foundation.

The authors have had the valuable assistance of Dr H. G. Epstein, a physicist whose work is already well known amongst anaesthetists. The subject matter is illustrated throughout by details of experiments and examples of calculations, all of which make for a clearer understanding of the principles described. Many original diagrams and drawings supplement the text. These are of the very high standard which one expects of Miss McLarty.

In the every-day work of the anaesthetist a certain amount of knowledge of the physical laws of gases and vapours is essential if modern anaesthetic procedures are to be carried through with adequate understanding and safety. It is probably true that most anaesthetists have forgotten most of what they learned about such things in the early part of their medical training. This book fills a great need in this respect,

not only for anaesthetists of all grades but also for the student who is about to commence his practical training in the administration of anaesthetics and is worthy of the highest commendation.

*Acidosis.* By ESBEN KIRK. Pp. 222. London: William Heinemann. 1946. (Price not stated.)

This book gives a detailed account of various aspects of the problem of acidosis. A historical survey is followed by a summary of the causes of acidosis. In the remaining sections of the book the various causes are considered in more detail, and illustrative cases are given from the author's own experience. Details of analytical technique are given and also a full list of references.

This book should be of interest to most physicians as it reminds them of the circumstances under which acidosis may occur, giving an explanation of the cause in each case, and draws attention to the benefits of rational therapy with isotonic sodium bicarbonate solution.

*Human Torulosis.* By LEONARD B. COX, M.D.(MELB.), M.R.C.P.(EDIN.), F.R.A.C.P., and JEAN C. TOLHURST, M.SC.(MELB.). Pp. xi+149, with 67 illustrations and 5 tables. Melbourne University Press and Geoffrey Cumberlege. 1946. Price 25s.

This monograph is based largely on the authors' personal experience of thirteen cases of human torulosis. These cases are reported in detail and in many cases include autopsy reports. In addition, there is a very full review of the subject from the clinical, pathological and epidemiological points of view. A detailed account is also given of the biology of the fungus and of laboratory methods of diagnosis. There are excellent photographs illustrating the radiological appearances in cases of lung involvement and both the macroscopic and microscopic appearances of the organs in man and in experimental animals. The morphology of the torula in the tissues and on culture is also demonstrated.

This work emphasises the importance of considering torulosis in obscure cases of cerebral or pulmonary disease. The unusual frequency with which these authors have encountered this disease suggests that either the infection is unusually prevalent in Australia or that elsewhere the disease is frequently misdiagnosed. Those requiring information on torulosis will certainly obtain every possible assistance from this book.

*Röntgen Diagnosis of Diseases of the Gastrointestinal Tract.* By JOHN T. FARRELL, Jr., M.D. Price 30s.

The author has adopted a very complete and somewhat complicated classification of diseases as a framework of his study. Such a classification one feels might have been more suitable for a larger volume in the nature of a text-book, and its adoption in a manual of this type has perhaps resulted in rather abbreviated accounts of the commoner conditions seen by radiologists in routine work. As a detailed classification of all the conditions which are demonstrable on radiological examination, however, this book offers a useful contribution to the literature on radiological diagnosis and the text is accompanied by good reproductions from radiographs.

*The Peripheral Circulation in Health and Disease.* By R. L. RICHARDS. Pp. xii+153, with 104 illustrations. Edinburgh: E. and S. Livingstone Ltd. 1946. Price 21s. net.

This concise handbook incorporates reviews of the anatomy and physiology of the peripheral vessels and a description of methods of investigation of the peripheral circulation, together with the records of personal observations, meticulously prepared, on a large series of cases. The whole presentation is carefully planned and admirably

executed, and the individual chapters are models of modern clinical scientific research. It is no fortuitous coincidence that the book opens with a quotation from Harvey and closes with one from Lewis. Accurate observation, logical deduction, and an absence of redundant hypotheses characterise the work throughout. The relative simplicity of the methods employed, and the rich harvest yielded, are in sharp contrast to much modern work in which increasing complexity of technical approach is only matched by the loose thought that attends the interpretation of results.

The production is excellent, and the figures well reproduced, but it is unfortunate that the lettering on so many figures has been reduced in reproduction to a size that renders easy reading difficult. The book is recommended not only as a valuable treatise on its special field, but as worthy of study by all who would engage in problems of clinical research.

*Aids to the Diagnosis and Treatment of Venereal Diseases.* By T. E. OSMOND, B.A., M.B., M.R.C.S., L.R.C.P. Pp. v+138. London: Ballière, Tindall & Cox. 1946. Price 5s. net.

This little book has been written for the purpose of instructing the medical student in the management of venereal disease. The subject has been dealt with by no means exhaustively, but enough information has been included to make this a useful handbook for students and practitioners.

*Entstehung und Früherfassung des Portiokarzinoms [Development and Early Recognition of Cervical Carcinoma.]* By Dr. med. Hansjakob Wespi, Zurich. Pp. 183, with 94 illustrations. Basle: Benno Schwabe & Co. 1946. Price Fr. 18.

This is a valuable monograph which, after an introductory section, is divided into two parts. In the first part there is set out with full clinical references the argument for colposcopy as a method in the early recognition of cancer of the cervix uteri. It is a highly practical text which lays stress on the *Schiller* iodine macroscopic diagnosis and illustrates abundantly the microscopic appearances of what the author classifies as superficial cancer and true cancer. The final development, as is shown in a schematic figure, is into immature, moderately mature and fully mature carcinoma. The author advocates frequent inspection after thirty years of age.

A considerable part of the work is devoted to theoretical considerations applicable to cancer anywhere. One interesting idea is embodied in the subdivision of the appearances of surface epithelium into (a) simple atypical, (b) unstable and (c) proliferative atypical epithelium. Many photomicrographs illustrate the very moderate views of the author. He touches on the theories of development of cancer by gradation and by somatic gene mutation without too absolute self-committal. He evidently favours multicentric occurrence of cancer and contact conversion of normal cells to cancer cells, which weight the probabilities to a causal virus agency. The references to the literature are well chosen and give the title throughout.

*Principles of the Contact Lens.* By H. TREISSMAN and E. A. PLAICE. Pp. vii+88, with 40 illustrations. London: Henry Kimpton. 1946. Price 10s. 6d. net.

One of the most important of modern developments in ophthalmic practice is the use of contact lenses. This little book, although dealing with a superspecialism, will be welcomed by all ophthalmic surgeons. The subject is clearly explained in nine short well-illustrated chapters. The second chapter, though mainly optical, is so well expressed as to offer no difficulty to the non-mathematical reader. The other chapters are practical and give a full and lucid description of the principles, construction, uses of, and indications for contact lenses with much valuable clinical information. Every ophthalmic surgeon, even if he does not prescribe contact lenses himself, will wish to have this book to guide him in the treatment of his patients.

## NEW EDITIONS

*Aids to Bacteriology.* By H. S. SCOTT-WILSON. Seventh Edition. Pp. 286, without illustrations. London: Ballière, Tindal & Cox. 1946.

This small book is most comprehensive in scope. It deals with general bacteriology, immunology, laboratory methods, disinfection, the bacteria, viruses, fungi and protozoa pathogenic to man, animals and plants, and the microbiology of soil, water, sewage and air. The treatment of some topics is naturally very limited, but much useful information is presented.

*A Synopsis of Surgical Anatomy.* By A. LEE MCGREGOR. Sixth Edition. Pp. xiii+714, with 699 illustrations. Bristol: John Wright & Sons Ltd. 1946. Price 25s.

In this new edition of a well-known text-book only minor alterations have been made. It contains much valuable information presented in a synoptic but very lucid manner which renders the book useful to both undergraduate and qualified students. The diagrams are prepared with a nice sense of the value of visual imagery.

Some details in the text may raise criticism. Removal of the adenomatous prostate, for example, should be described as enucleation from a false capsule of compressed gland tissue, and not as enucleation of the gland from its own true capsule as elaborated by the author. It is disappointing too, in this sulphonamide era, to encounter the categorical statement that no drug except urotropine is secreted into the cerebrospinal fluid.

Such minor faults are, however, few; the author's statements are, on the whole, remarkably reliable and the book well deserves its continued popularity.

*Textbook of Gynaecology.* By ARTHUR HALE CURTIS, M.D. Fifth Edition Revised. Pp. xvi+755, with 455 illustrations, 36 in colour. London: W. B. Saunders Company Ltd. 1946. Price 40s. net.

The fifth edition of this well-known American text-book has undergone extensive revision. New matter has been added especially in the sections dealing with ovarian tumours, endocrine disturbances and gonorrheal infections. Two new subjects are included in the chapter on "Other Tumours of the Uterus." One is sarcomatoid growth of the endometrial stroma (stromal endometriosis of Goodall) and the other, hypertrophy of the uterus, embraces chronic sub-involution, chronic metritis and diffuse hypertrophy.

Generously illustrated with plates, drawings, photographs and microphotographs, all beautifully reproduced, it gives a clear and well-balanced presentation of modern gynaecology from both the pathological and clinical aspects. This is enhanced by frequent reference to the author's own experience, considered opinion and present practice in the handling of problems. In this connection it is interesting to note that the author has never found it necessary to employ an operation such as Studdiford describes for stress incontinence of urine, as a vaginal plastic operation is always possible, and, in his hands, successful in relieving this distressing complaint. Again it must be very unusual to find complete absence of tenderness of a pregnant tube, especially after tubal abortion or rupture, although the text conveys the opposite impression.

There is a useful up-to-date bibliography at the end of each chapter, and a feature of the book is the section on anatomy written from the applied and clinical standpoint. Gynaecologists will find this edition most useful.



*X-rays and Radium in Diseases of the Skin.* By GEORGE M. MACKEE, M.D., and ANTHONY C. CIPOLLARO, M.D. Fourth Edition. Pp. 668, with 321 engravings and 4 coloured plates. London: Henry Kimpton. 1946. Price 50s. net.

In the previous edition MacKee had several collaborators but now has one of these as co-author. This edition has 160 pages fewer than the last, but this has been achieved by cutting out some of the less essential paragraphs and without diminishing the value of the book. For example, the plant for collecting radon is no longer described.

The authors stress and deplore the tendency in some quarters to use X-rays too freely and to the exclusion of other remedies, especially the more modern ones. It is their opinion that the dermatologist and not the radiologist should treat diseases of the skin as the diagnosis is more likely to be correct when made by the former, and that therefore there is less risk of a condition, not suitable for X-ray treatment, being subjected to this form of therapy. With this opinion the reviewer heartily concurs. The book is still the standard work on this subject and should be in the library of every dermatologist.

*Medical Electricity for Massage Students.* By HUGH MORRIS, M.D., D.M.R.E. Third Edition. Pp. viii+348, with 114 illustrations. London: J. & A. Churchill Ltd. 1946. Price 21s. net.

Dr Morris, in this edition of his text-book, has revised and rewritten the whole text. He has now presented a simple but complete exposition of the subject as required for the Electrotherapy examination of the Chartered Society of Physiotherapy.

The early chapters deal with physics and simple chemistry, cells and batteries and apparatus. Later chapters describe in detail the production of high-frequency currents and indications for their use, and finally the production of ultra-violet radiation, their effects on the body and chemical uses.

A useful glossary is appended which will prove very valuable to the student.

The whole text is clear and well illustrated, and will prove a useful text-book for all who are interested in electrotherapy.

*Principles of Hematology.* By R. L. HADEN, M.A., M.D. Third Edition. Pp. 366, with 171 figures. London: Henry Kimpton. 1946. Price 25s. net.

This book has been written as a simple discussion of the fundamental principles of the subject to make it accessible to the student and general practitioner. Technical procedures are given clearly in considerable detail. The book describes the normal physiology of the blood and the mechanisms of various disordered processes as well as the principles of treatment. Several chapters are devoted to the various diseases of the blood, the clinical pictures being illustrated by records of typical cases. A useful book for the practitioner who is specially interested in this field of medicine.

*The M.B., B.S. Finals.* By FRANCIS MITCHELL-HIGGS, M.B., B.S., F.R.C.S. EDIN. Third Edition. Pp. xvi+98. London: J. & A. Churchill. 1947. Price 8s. 6d.

In this edition the author presents the collected papers of the final examinations of London University from 1932 to 1945. The questions have been classified under general headings. This small book should prove useful to medical students working for the final examinations of all Universities.

*Demonstrations of Physical Signs in Clinical Surgery.* By HAMILTON BAILEY, F.R.C.S., F.I.C.S. Tenth Edition Revised. Pp. xii+375, with 573 illustrations. Bristol: John Wright and Sons Ltd. 1946. Price 30s. net.

Ten editions with seven reprints in less than twenty years is a remarkable achievement for any book. The author has taken great pains to introduce improvements

and acknowledge helpful suggestions from many friends. In particular, the illustrations, which form such an attractive feature of this work, have been thoroughly reviewed and many new ones have been included. This remarkable work, now being translated into several foreign languages, will continue to make a strong appeal to the medical profession.

*Dental Materia Medica, Pharmacology and Therapeutics.* By WALTER J. DILLING, M.B., CH.B. ABERD., M.P.S. (HON.), and SAMUEL HALLAM, L.D.S., R.C.S. ENG. Third Edition. Pp. xvi+360. London: Cassel & Co. Ltd. 1946. Price 13s. 6d.

In this edition the book has undergone revision and amendments, and additions to the text have been made to incorporate recent advances in dental science.

The sulphonamides and penicillin are now included in a section on special antiseptic agents, but the dental methods of application do not include the use of sulphonamide penicillin mixtures—a combination of drugs which is proving to be of considerable value in the dental field. The influence of fluorides upon the incidence of caries is briefly stated and this should prove of value to those who require a short summary of existing knowledge. Some of the statements made with regard to plaster of Paris might be misleading to students, and this section could have been omitted as details of the substance are adequately dealt with in books on dental materials.

The general lay-out of the book is good, information is readily available and useless repetition is avoided. The book can be recommended as of educational value to dental students and as a handbook of reference to the busy practitioner who has little time to spare to peruse more voluminous works.

*Aids to Tropical Hygiene.* Edited by L. NICHOLLS, C.M.G., B.A., M.D. Third Edition. Pp. xii+217. Illustrated. London: Dailière, Tindall & Cox. 1946. Price 6s.

The editor draws attention to the profound changes that have taken place in tropical practice since the First World War. New ideas on food and nutrition have made these subjects of increasing importance for those who work in the tropics. Tropical hygiene has now become so large a field that each branch must be dealt with by experts. The book has been written in three sections—Parasitology, Nutrition and General Public Health work—each entrusted to a specialist on the subject.

*Pulmonary Tuberculosis.* By R. N. KEERS, M.D., M.R.C.P. (EDIN.), F.R.F.P.S. (GLAS.), and B. G. RIGDEN, M.R.C.S., L.R.C.P. Second Edition. Pp. xvi+277, with 124 illustrations. Edinburgh: E. & S. Livingstone. 1946. Price 17s. 6d.

In the second edition of this small book the authors have presented a concise picture of the present position of pulmonary tuberculosis. In recent years the work of Rich has clarified some of the debatable points concerned with the pathogenicity of the disease, and his views have been included in the chapters on Pathology and Resistance. The section of B.C.G. Vaccine has been expanded in view of the recent Scandinavian work. The small handbook offers a comprehensive account of the subject.

*Gray's Anatomy.* Twenty-ninth Edition. Edited by T. B. JOHNSTON, C.B.E., M.D., and J. WHILLIS, M.D., M.S. Pp. xix+1597, with 1359 illustrations. London: Longmans, Green & Co. 1946. Price 70s. net.

*Gray's Anatomy* has been extensively revised, and new matter introduced in the sections on Embryology and Neurology. There are nearly 200 new illustrations. This new edition, so well written and produced, inevitably induces the Edinburgh reader to make comparison between it and *Cunningham's Anatomy*. Is there any reason why one should be preferred to the other? Both books are well presented,

thoroughly authoritative and complete; and as regards size and weight, number of pages, and number and attractiveness of the illustrations, the books are almost identical. The X-ray plates in both are a pleasure to study. Cunningham, Eighth Edition, 1943, is slightly cheaper—60s. Some may find the type of Cunningham rather easier to read—the letters are 1.5 mm. in height in Cunningham and 1.25 mm. in Gray, and the lines are 2.5 mm. apart in Cunningham and 2 mm. in Gray. The paper of Cunningham is rather more opaque and there is less tendency for illustrations of the previous page to shine through.

But these are small points, and no doubt the choice of text-book will continue to be influenced by custom and loyalty. Certainly both books are a credit to British Anatomy, and this new edition of *Gray's Anatomy* deserves the highest praise.

*Clinical Haematology.* By M. M. WINTROBE, M.D., PH.D. Second Edition. Pp. 862, with 197 figures and 14 plates. London: Henry Kimpton. 1946. Price 55s. net.

Advances in hæmatology have been so rapid recently that it has been necessary to rewrite a very considerable amount of this book. There is an entirely new chapter on the metabolism of the erythrocyte, and many new illustrations have been added. Folic acid, the nitrogen mustards and the Rh. factor have been fully discussed.

Professor Wintrobe's book is easily the most authoritative on the subject at the present time.

## BOOKS RECEIVED

- ASCHNER, BERNARD, M.D. *The Art of Healing.*  
(*William Heinemann Medical Books Ltd., London*) 12s. 6d. net.
- DAVIDSON, L. S. P., B.A. (CANTAB.), M.D. (EDIN. and OSLO), F.R.C.P. (EDIN. and LOND.), F.R.S.E., and ANDERSON, IAN A., M.B.E., B.Sc. (ABERD.), M.B., CH.B. (ABERD.). *A Textbook of Dietetics.* Second Edition.  
(*Hamish Hamilton Medical Books, London*) 21s. net.
- DOGGART, JAMES HAMILTON, M.A., M.D. (CANTAB.), F.R.C.S. ENG. *Diseases of Children's Eyes.*  
(*Henry Kimpton, London*) 42s. net.
- GEIKIE-COBB, IVO, M.D. *The Glands of Destiny.* Third Edition.  
(*William Heinemann Medical Books Ltd., London*) 15s. net.
- Edited by GLUECK, BERNARD, M.D. *Current Therapies of Personality Disorders.*  
(*William Heinemann Medical Books Ltd., London*) 17s. 6d. net.
- Edited by GREENHILL, J.P., B.S., M.D., F.A.C.S. *The 1946 Year Book of Obstetrics and Gynecology.*  
(*The Year Book Publishers Inc., Chicago*) \$3.75
- MONRAD-KROHN, G. H., M.D., F.R.C.P. *The Clinical Examination of the Nervous System.* Eighth Edition.  
(*H. K. Lewis & Co. Ltd., London*) 16s. net.
- NICOLE, R. *Metallschädigung bei Osteosynthesen.*  
(*Benno Schwabe & Co., Basel*) 8 Swiss francs.
- OCKERBLAD, NELSE F., B.S., M.D., F.A.C.S. *Urology in General Practice.* Second Edition.  
(*The Year Book Publishers Inc., Chicago*) \$5.75
- STRACHAN, GILBERT I., M.D., F.R.C.P., F.R.C.O.G. *Textbook of Obstetrics.*  
(*H. K. Lewis & Co. Ltd., London*) 45s. net.
- SPIES, TOM D., M.D. *Rehabilitation through Better Nutrition.*  
(*W. B. Saunders Company, London*) 20s. net.
- SPIESMAN, MANUEL G., B.S., M.D. *Essentials of Clinical Proctology.*  
(*William Heinemann Medical Books Ltd., London*) 21s. net.
- VON ANDICS, MARGARETHE. *Suicide and the Meaning of Life.*  
(*William Hodge & Co. Ltd., London*) 8s. 6d. net.
- WARKENTIN, JOHN, PH.D., M.D., and LANGE, JACK D., M.S., M.D. *Physician's Handbook.* Fourth Edition.  
(*University Medical Publishers, Chicago*) \$1.50
- WILLENEGGER, Dr H., and BOITEL, Dr R. *Der Blutspender.*  
(*Benno Schwabe & Co., Basel*) 10 Swiss francs.
- WUHRMANN, F., and WUNDERLY, CH. *Die Bluteiweisskörper des Menschen.*  
(*Benno Schwabe & Co., Basel*) 36 Swiss francs.
- ZETA. *The Diagnosis of the Acute Abdomen in Rhyme.*  
(*H. K. Lewis & Co. Ltd., London*) 5s. 6d. net.

# Edinburgh Medical Journal

June 1947

## GROWTH IN RELATION TO MATURITY \*

By RICHARD W. B. ELLIS

*From the Department of Child Life and Health, University of Edinburgh*

THE intensive study of child and adolescent development during the present century has made it possible to lay down certain "normal" or average standards related to chronological age. These include standards of intelligence, behaviour (Gesell, 1928), ossification (Todd, 1937), hormonal excretion (Nathanson *et al.*, 1941; Talbot *et al.*, 1943), and the various aspects of physical growth. Since a study of individual children from birth to maturity implies an experimental period of not less than twenty years, most investigators have preferred to base their conclusions on mass studies of children in each annual, six-monthly, or monthly age-group, and to construct, for example, height and weight curves in which the same individuals may be represented at only a single point on the curve. These curves have a considerable value in comparing large groups of children in different environmental conditions, or in different epochs, or of different races. Thus in the London County Council area it had been shown (Menzies, 1940) that both the mean height and the mean weight of school children at all ages from 5 to 14 years were substantially greater in 1938 than in 1905-12, and also that the figures for 1942 and 1943 in the south-western division of London were again higher than the corresponding figures for 1938 (Daley, 1944). That so-called "normal" height and weight curves may become out of date comparatively rapidly was further exemplified by an investigation of the growth of Belgian school children living in a working-class commune in Brussels during and after the German occupation (Ellis, 1945). Mean height and weight curves for all children attending school and examined during the autumn term were prepared for 1942 (the most severe period of nutritional deprivation), 1943, when conditions had slightly ameliorated owing to a national distribution of herrings and organisation of the Black Market, and 1944 (immediately after the liberation). These were compared with the standard height and weight curves in use for school medical records in Belgium with the rather surprising result that although at most ages the mean heights and weights in

\* A Honyman Gillespie Lecture delivered on 20th February 1947.

1942 were slightly below the standard, in 1944 they were slightly above. Further enquiry showed that the standards, though published in 1934 by the Ministère de l'Instruction Publique, had been prepared from children throughout the country some years earlier, following a period of economic depression. Sampling of the school medical records in the same commune for the years 1938-39 then showed that at all ages tested the mean heights and weights of school children immediately before the war were substantially higher than the earlier standards, and indicated, as would be expected, that there had been a significant falling off during the war years.

TABLE I

Age (Years).	Height (cm.).			Weight (kgm.).		
	1938-9 (sample).	1944.	1934.	1938-9 (sample).	1944.	1934.
Boys						
7-8	125.0	121.1	117.6	24.2	22.2	22.0
9-10	132.1	131.0	127.7	27.3	26.8	25.6
11-12	142.8	139.0	136.7	34.2	32.1	31.1
13-14	151.0	147.7	145.5	41.0	38.8	36.4
Girls						
7-8	122.2	120.6	116.8	23.8	21.7	21.4
9-10	130.0	128.4	126.6	26.4	25.2	25.1
11-12	144.0	138.0	136.5	36.0	31.1	30.4
13-14	151.0	149.9	148.7	44.0	41.7	39.3

In addition to their value in comparing the nutritional and developmental status of large groups of children, mean height and weight curves allow certain crude generalisations with regard to their general shape. Thus there is a rapid increase in both height and weight during infancy, and a rapid deceleration, particularly in growth in height, as adulthood is approached. It is also found that whereas boys are on the average heavier and taller than girls in similar circumstances for the greater part of their lives, there is a period of approximately  $2\frac{1}{2}$  to 3 years ( $11\frac{1}{2}$  or 12 to 14 or 15) during which girls are on the average heavier and taller than boys. This is attributed to the earlier onset of sexual maturity in girls, to which further reference will be made.

Returning to the figures for Belgian children during the period of nutritional deprivation, it was found that the curves for the younger age-groups were essentially similar in shape. In comparing the mean weight of girls over 12, however, a striking difference was seen between the curves for 1942, 1943 and 1944.

Thus in 1942 there is a steep rise in weight between the ages of  $14\frac{1}{2}$  and  $15\frac{1}{2}$ , in 1943 between  $13\frac{1}{2}$  and  $14\frac{1}{2}$ , and in 1944 between  $12\frac{1}{2}$  and  $13\frac{1}{2}$  years, the final weights being almost identical. Although as

emphasised when the original data were presented, the numbers in each group are too small and the clinical data too incomplete to allow any categorical statement, the shape of these curves suggests that the age of puberty, with its associated weight-increment, was most delayed during the period of severest restriction (1942), becoming earlier with progressively more adequate diet. That such a retardation of puberty occurs during periods of under-nutrition has been suggested by a number of observers in the occupied countries. Menstrual histories taken from 64 older girls living in the commune studied in 1945 gave confirmatory evidence of delayed menarché and establishment of regular menstruation during the war years. It was unfortunate that no record of the menstrual history was given in the school medical

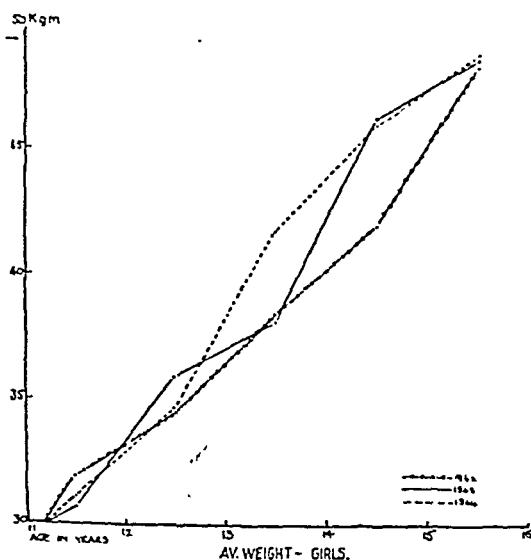


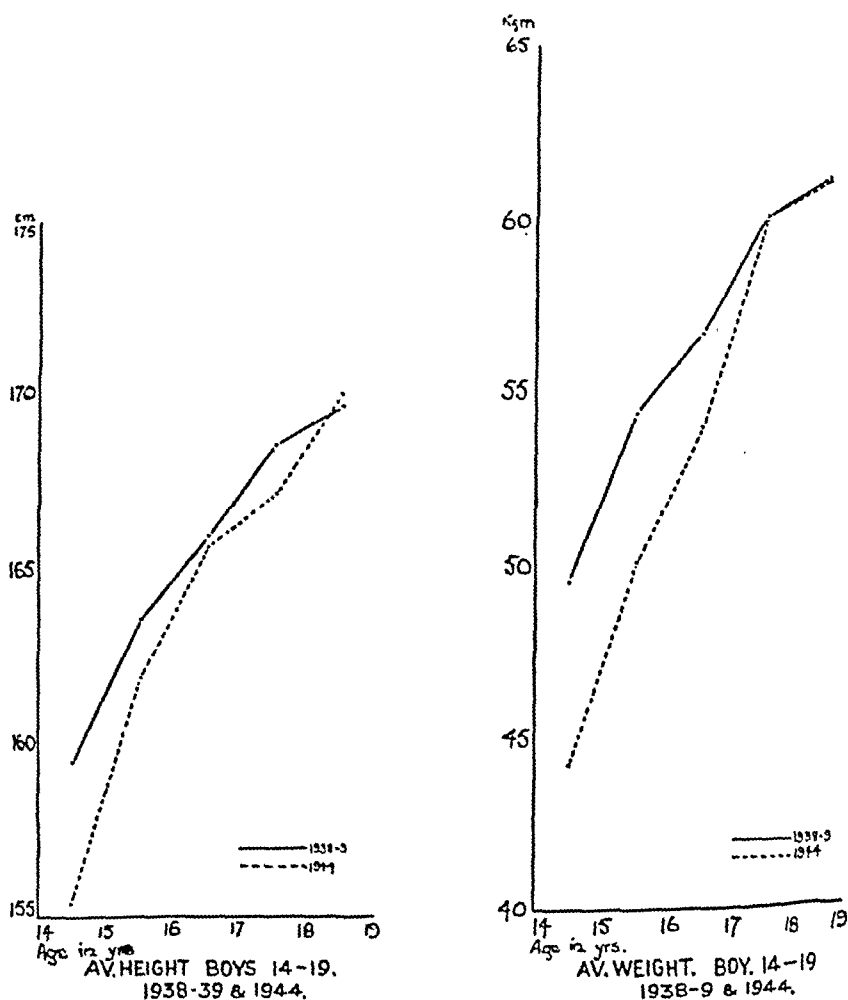
FIG. 1.—Mean weight of girls aged 11 to 16 in 1942, 1943 and 1944.

records of the older girls included in the mean height and weight curves given above, and that no accurate correlation could be made between the growth curves in the years under review and the mean age of menarché, nor comparison made with the mean age of menarché in 1938-39.

Since the number of boys attending school after the age of 14 was too small in each year to allow statistical analysis, a comparison was made between the height and weight curves of boys in Government employment as telegraph boys in the years 1938-39 and 1944, again dividing subjects into yearly age-groups.

These curves show the interesting fact that whereas the younger age groups are substantially smaller after the prolonged period of malnutrition, the final height and weight are almost identical in the 18-19-year-old boys in the two periods. Since the nutrition of adolescents

(who were, for instance, ineligible for any milk except in case of illness) was much more inadequate than that of school children, it might at first sight have been expected that the oldest boys, *i.e.* those who had suffered two to three years of severe malnutrition, would have showed the greatest and not the least difference from the normal. Although there are a number of uncontrolled factors which might help to account for this apparent anomaly, it is suggested that the most probable



FIGS. 2 and 3.—Mean height and weight of Belgian telegraph boys aged 14 to 19, in 1938-39 and 1944.

explanation again lies in the age of onset of puberty. Whereas the great majority of boys who were 18-19 in 1944 would have reached puberty and have embarked on or completed their period of most rapid growth by the time the food supplies had reached their lowest point in 1942, a delay in the age of onset of puberty due to malnutrition might well account for the findings in the lower age groups.

It was found impossible to check this hypothesis, since the medical records of these boys, though exceptionally full with regard to assessment of physical fitness, omitted all reference to the stage of maturity

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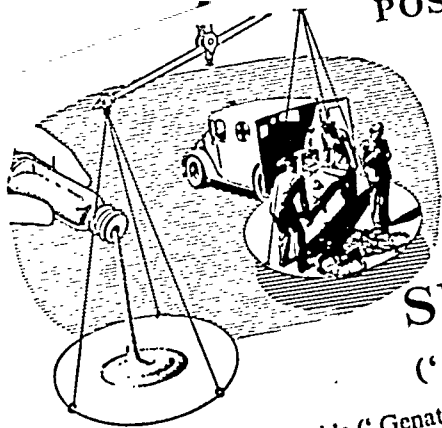
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at each examination. This is true of almost all routine medical records of boys not only in Belgium but also in Great Britain, and it was felt that if, as is generally agreed, the age of onset of puberty affects the growth curves of the individual child, it was highly desirable to determine first the normal range of age-onset of puberty and secondly whether this could be correlated with the shape of composite growth curves.

Before considering the standards employed for this purpose, it should be explained that "puberty" is here used to describe the transition period between childhood and adolescence, beginning with the appearance of manifest primary and/or secondary sexual characters (e.g. genital development, breast development, and appearance of pubic hair) and terminating with ovulation or spermatogenesis.

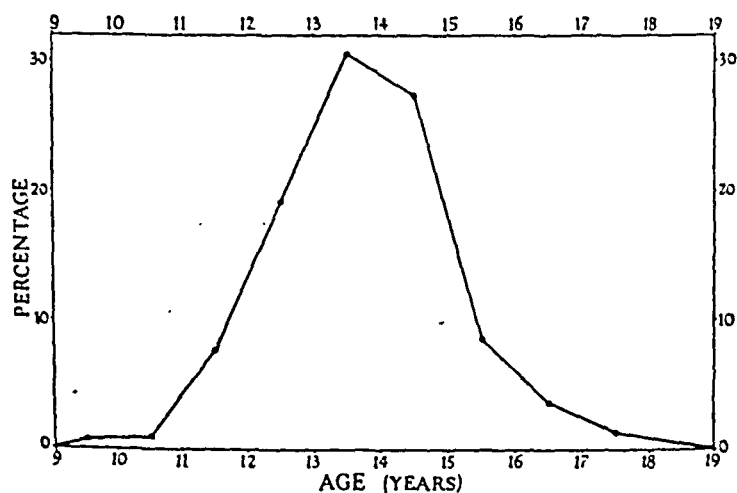


FIG. 4.—Distribution curve showing percentage of 470 subjects first menstruating in each year of age.

Adolescence then dates from the onset of ovulation or spermatogenesis to the establishment of full physical maturity, and is characterised by relative infertility and continued growth. Most of the studies of growth in relation to puberty have been carried out on girls, using as a criterion the age of onset of menstruation. This has obvious advantages from the statistical point of view, since the first menstrual period is often recorded or its date remembered retrospectively. It should be realised, however, that the first menstrual period is not necessarily coincident with the onset of ovulation, and may be followed either by regular menstruation or by more or less prolonged periods of amenorrhœa.

If we take this criterion for what it is worth, however, it is at once obvious that the range of age-onset of menstruation in normal subjects is very wide.

The above distribution curve is based on figures kindly supplied

by Dr P. M. Bishop from answers to a questionnaire by 470 British nurses who had passed a medical examination before training, and shows the percentage menstruating for the first time in each year-age group. Whilst the average age is 13.73 years, and in 77.1 per cent. the menarché falls between 12 and 15 years, it will be seen that in

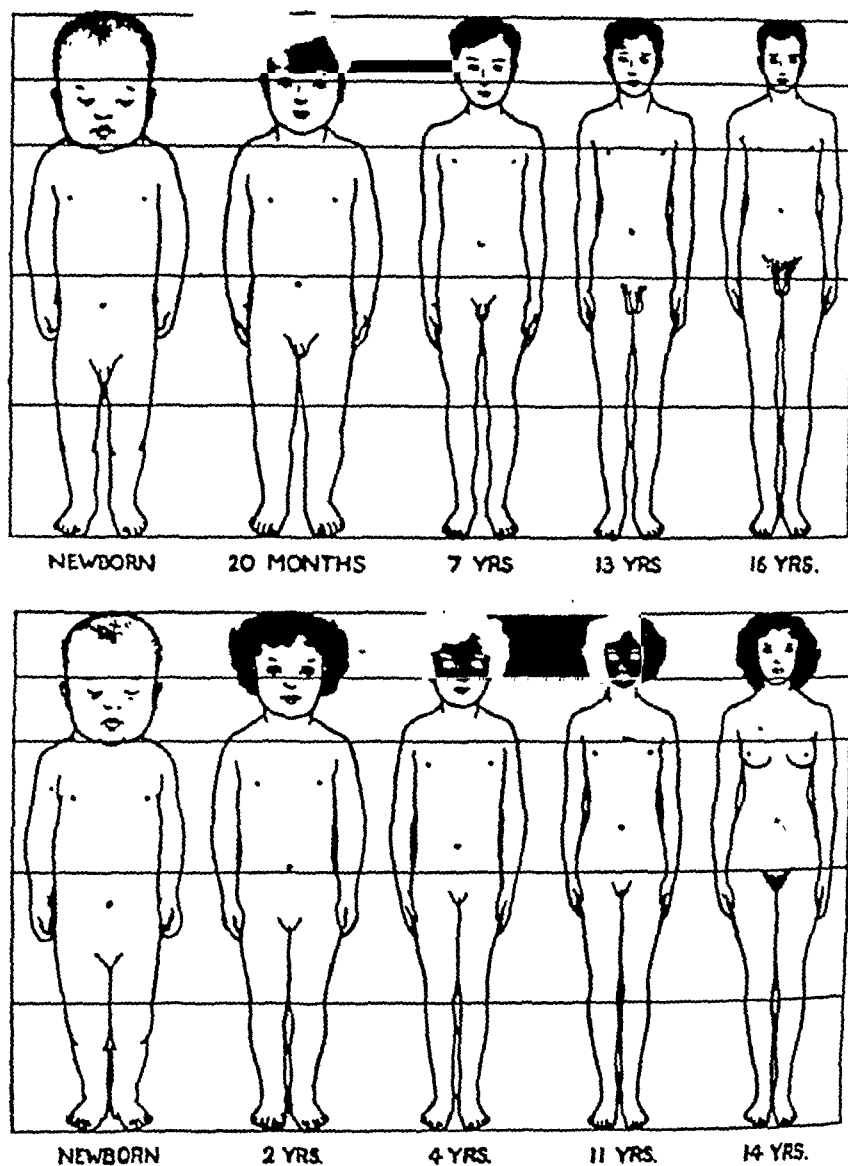


FIG. 5.—Diagrams showing relative proportions, from birth to adolescence.

3 cases menstruation first occurred between 9 and 10 years, and in 2 cases between 18 and 19 years. If therefore there is in the individual a characteristic increment in height or weight directly related to the onset of puberty, it will tend to be smoothed out in composite height and weight curves which take no account of the age of onset of puberty in the subjects included.

So far I have referred to growth only in its simplest terms, viz.

increment in height and weight of the body as a whole, and whilst the present study is concerned primarily with these two factors, it should be emphasised that increasing maturity is characterised by changes in the relative proportions of the body and that the growth of individual tissues (neural, lymphoid, and genital) follows different developmental lines (Scammon, 1930). The changes in relative proportions are illustrated in Fig. 5 which have been constructed from photographs of children from birth to adolescence.

It will be seen that whereas in the newborn infant the head represents a quarter of the total length and the legs approximately three-eighths, in adolescence the proportions are one-seventh and one-half respectively. The umbilicus, which lies well below the midline in the newborn, in the adolescent lies one-eighth of the total height above.

Radiological study of ossification has done much to clarify the state of maturity of the individual child, and it has been shown that wide differences may exist not only between boys and girls of the same ages, girls in general being in advance of boys, but also between different individuals of the same sex and age. To take two extreme examples, where the retardation of development is pathological: Fig. 6 shows a case of infantilism of Lorain type standing beside a normal boy of the same age ( $16\frac{1}{2}$  years). The patient with infantilism is of approximately the size and relative proportions of a normal boy of nine years of age; Fig. 7 shows the contrast between the ossification of the hands of these two boys. Not only are the size and density of calcification much less in the case of the infantile, but the ossification of the carpus is less advanced, and there is entire non-union of the epiphyses of the radius, ulna, metacarpals and phalanges. The second example is that of a young man of 26 years, suffering from pituitary infantilism, whose height is that of a boy of approximately 13 years, with infantile genitalia, girdle distribution of fat, absence of secondary sexual characters, height 147.5 cm., weight 48 kg. The radiograph of the hand (Fig. 8) shows non-union of the radial, ulnar, metacarpal and phalangeal epiphyses. In normal subjects, radiological examination may show as much as four years' difference in the stage of ossification of patients of the same age during the early 'teens, depending on the late or early onset of puberty. Harris (1947) has drawn attention to the close correlation between the beginning of fusion of the triradiate cartilage of the hip and puberty, and Flory (1935) describes the appearance of the sesamoid bone of the distal end of the first metacarpal as the most useful radiological finding in prognosing the onset of puberty in girls.

Any complete assessment of maturity of the individual child should therefore include not only the clinical examination and measurement, but also radiological examination. To these should be added the assay of oestrogen, androgen, and gonadotrophic hormonal excretion, though here the practical difficulties at present make this line of investigation of limited application.

It has already been pointed out that whereas in the case of girls there is ample information available with regard to the age of menarché, which can be, and in many instances has been, related to the growth curves, in the case of boys very little accurate information has been collected in Great Britain either with regard to the age of onset of puberty or its effect on growth. In France, Godin (1927) carried out serial examinations of a large number of school children and adolescents over many years, and in America the subject has recently been put on to a more scientific basis by the Society for the Study of Child Development (Greulich *et al.*, 1938, 1942). Unfortunately Greulich's monograph on adolescent boys was not available in this country when the present study was undertaken, but it was found subsequently that similar criteria for the clinical assessment of maturity had been used, although three instead of five maturity grades were recognised. The purpose of the investigation was to see whether, in the first instance, simple clinical standards of maturity-grading of boys in relation to puberty could be devised, and if so whether maturity-grading, irrespective of chronological age, threw any light on the height and weight curves of the subjects examined.

A more detailed description of the standards used in maturity-grading has been given elsewhere (Ellis, 1946) but briefly they were as follows. Boys were graded as "non-pubescent" \* if genital development was minimal or infantile and if pigmented pubic hair was entirely absent. The grading "pubescent" was used for boys showing early genital development, *i.e.* growth in length of the penis without well-marked development of the corpora cavernosa, recognisable increase in size of the testicles in relation to the epididymis (which latter, in the child, is relatively much larger compared with the testis than in the adolescent), greater peripheral than proximal width of the scrotum, and/or the presence of coarse, pigmented pubic or axillary hair. It was found that the appearance of pubic hair and genital development, either of penis or scrotum, were not necessarily synchronous in early pubescence, and the grading of pubescence was given when any one of these signs was unmistakably present. (It was rare to find the growth of axillary hair preceding that of pubic hair, but it was observed in two instances before obvious genital development had occurred). The grading "adolescent" was given when genital development was well advanced, *i.e.* development of corpora cavernosa, and enlargement of testicles together with peripheral widening of scrotum, associated with the presence of pubic hair.

Two hundred and eight boys, from two residential schools, were examined in the first instance, and graded irrespective of chronological age. Admittedly some difficulty was found in grading border-line cases, since one stage of maturity will change gradually and not abruptly to the next, but these only represented a small proportion of the total.

\* The term non-pubescent has here been preferred to "prepubescent" originally used (Ellis, 1946), in order to avoid confusion with the nomenclature of other authors.

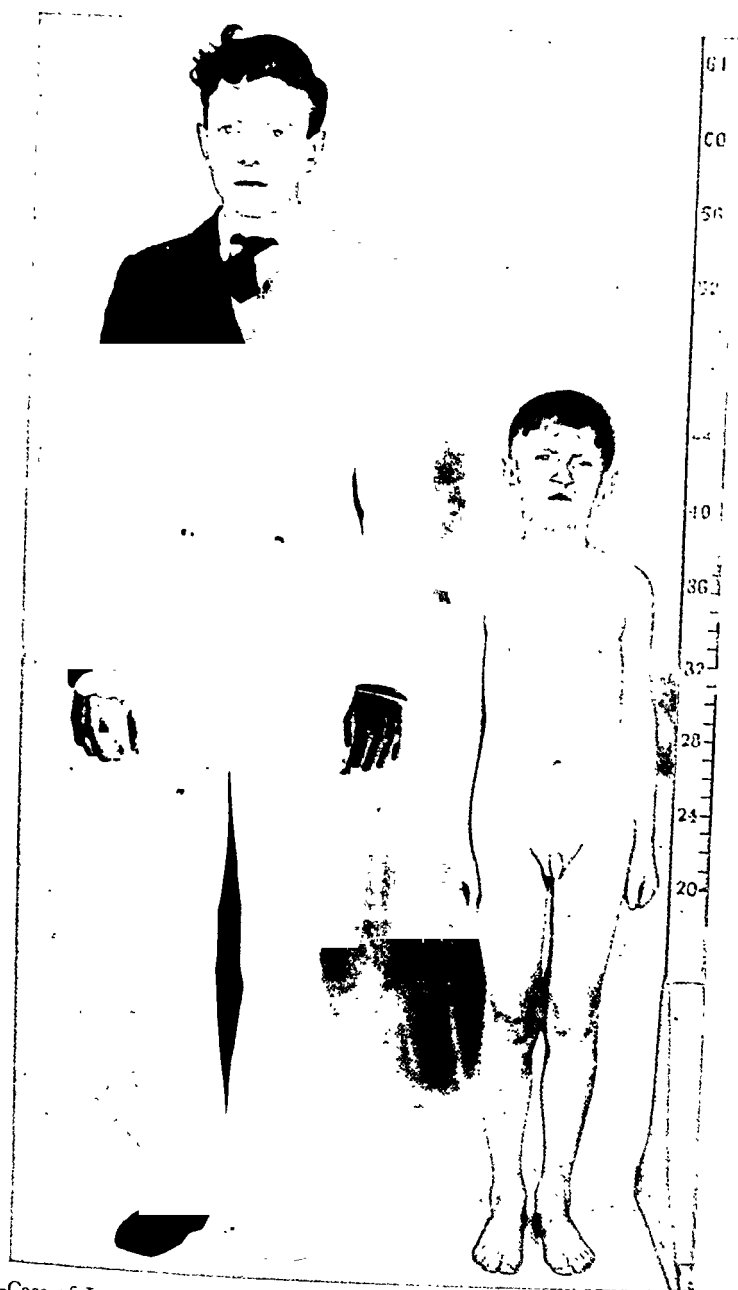


FIG. 6.—Case of Lorain infantilism, with hare-lip and cleft palate, beside normal control, both aged  $16\frac{1}{2}$  years.

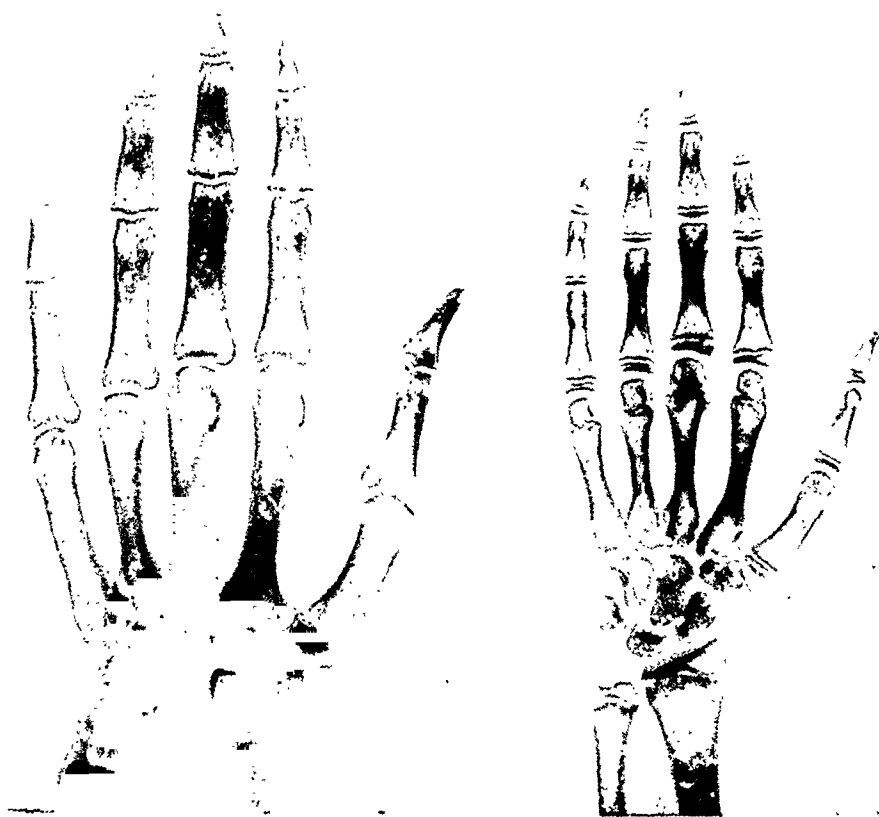


FIG. 7.—Radiograph of hands of the same two boys. That of the infantile shows not only smaller size but delayed ossification of carpus, and absence of fusion of epiphyses.

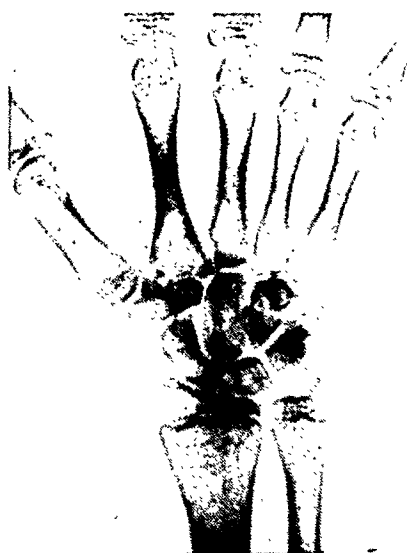


FIG. 8.—Radiograph of wrist of patient with pituitary infantilism. Age 26 years; height 147.5 cm.; weight 48 kg.; infantile genitalia and absence of secondary sexual characters. Note ununited epiphyses of radius, ulna, metacarpals and phalanges.

In order to test the validity of the grading, a second examination of 132 of the boys was made a hundred days later without reference to the first. It was found that eleven subjects had then been placed in a higher grade, in view of their more advanced development in the interim, and in no instance was a boy given a lower grading than on the previous examination. It was therefore considered that this method of purely clinical assessment had a certain value in determining stages of increasing maturity if its limitations were clearly recognised. The "non-pubescent" group, for instance, would include boys who were virtually infantile and also boys within two or three months of manifest puberty, in whom readjustment of endocrine balance might be expected to be occurring; similarly the "adolescent" group showed a wide range of development from early to late adolescence. It was found that Greulich *et al.* (1944) had in fact recognised five maturity grades, but though this is scientifically more satisfactory, the number of grades employed will obviously add to the difficulties of their clinical application.

*Age of Onset of Puberty.*—In order to determine this accurately, it would be necessary to follow the same group of boys over a number of years and record the first manifestations of puberty as they occurred. The following table shows the percentage of each age-group examined who were graded as prepubescent, non-pubescent, pubescent and adolescent. The figures are based on 662 examinations, the clinical material being drawn from the two residential schools referred to, and supplemented by 101 boys aged 14 to 18, in two residential homes for working boys.

TABLE II

*Distribution of Maturity in Boys aged 9 to 18 Years*

Age (years).	No. Examined.	Non-pubescent (per cent.).	Pubescent (per cent.).	Adolescent (per cent.).
9-10	52	100.0	0.0	0.0
10-11	40	95.0	5.0	0.0
11-12	74	86.5	13.5	0.0
12-13	95	64.2	35.8	0.0
13-14	135	47.4	43.7	8.9
14-15	120	12.5	39.2	48.3
15-16	78	1.3	29.5	69.2
16-17	33	6.1	18.2	75.7
17-18	35	0.0	11.4	88.6

Shown graphically (Fig. 9) it will be seen that "pubescence" in these boys has an age-distribution somewhat similar to that of the onset of menstruation in girls, though representing an earlier stage of development, and bearing out the earlier maturity of girls as compared with boys. (The fact that the curve is unequally distributed on either side the peak at 13.5 years is possibly related to the fact that the older age-groups were largely composed of boys from a



different environment and nurture than those in the two residential schools; but the distribution is in fact more nearly lognormal, which Gaddum (1945) has shown is a not uncommon finding in dealing with biological data.) Boys over 18 were not included as the small group examined had been excluded from military service for various reasons, including poor general physique and could not therefore be regarded as a normal sample. The examination served to show, however, that pubescence might occasionally be seen in boys aged 18-19 without evidence of endocrine or other disease.

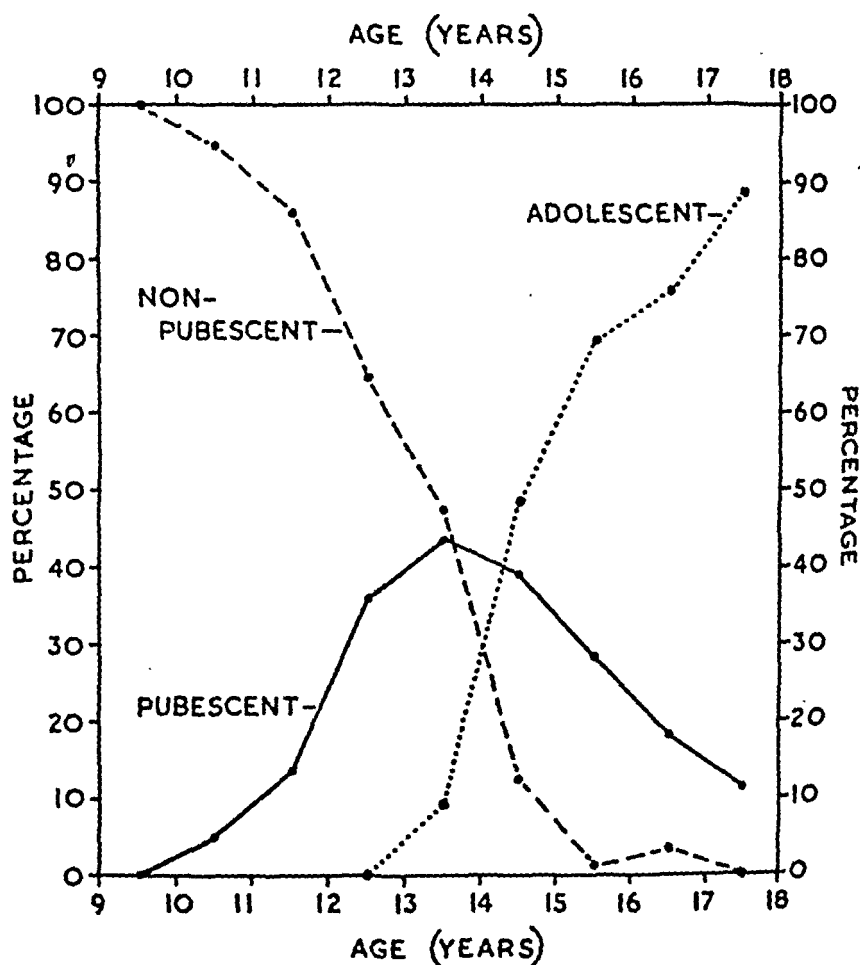


FIG. 9

Fig. 9 also illustrates the effect which raising the age of compulsory school attendance from 14 to 15 is likely to have on the maturity of boys entering employment. Whilst at 14 the percentage of completely immature boys is actually greater than the percentage graded as adolescent, at 15 years the percentage of "non-pubescent" boys is less than 10, whilst that of adolescents has risen to nearly 60.

*Height and Weight related to Onset of Puberty.*—Having graded the original 208 boys on a maturity basis irrespective of chronological

age, it was then possible to compare the mean height and weight of boys in a higher maturity grade with those of boys of the same age but who were less mature. Thus pubescent boys aged 12 to 13 years could be compared with non-pubescent boys also aged 12 to 13, and adolescents aged 14 to 15 could be compared with pubescent boys of the same age. Although the two residential schools from which the boys were selected were comparable as regards diet and living conditions (which were good in both instances), it was thought best to use as controls only boys from the same school. Whilst this rendered the groups comparatively small, it avoided a number of possible errors and it was found in fact that the results in both schools were essentially the same. School A was exceptionally well suited for a controlled experiment of this type, as the boys all entered from foster homes at the age of five, and had been weighed and measured annually by trained personnel from that age to the date of examination. All received the same diet, and until 1945 all had remained in the school throughout the year. In school B the boys entered from their own homes at different ages, so that complete records were not available for as many years as in school A, and returned home during the holidays. Here again regular weighing and measuring had been carried out by trained personnel.

An initial comparison of the mean heights and weights of boys in the same year-age group but in different maturity groups showed that in every age-group the more mature boys were the taller and heavier. Details of these figures, including the standard deviation and standard error in each instance are given elsewhere (Ellis, 1946), and I will here only illustrate the findings graphically. Having established that these differences were significant, composite growth curves were constructed for the higher and lower maturity-groups within each age-group where the numbers of subjects were sufficient to make comparison possible. The following graphic representations make allowance for minor differences in average age within the year-age group.

It will be seen that in the case of school A, where measurements were available to the sixth year, differences between the mean height and weight of the non-pubescent and pubescent boys who were aged 12 to 13 at the time of the examination were present in the sixth year, *i.e.* long before any of the direct effects of puberty could be operative; this also applied to the boys aged 13 to 14 at the time of examination. In the case of boys at school B, also aged 13 to 14 at the time of examination, the findings were essentially similar, though the records did not extend back to as early an age.

Comparison of the pubescent and adolescent boys (school B) shows a greater quantitative difference in mean height and weight at the time of examination, and the shape of the curves suggest that puberty is associated with a rapid gain, particularly in weight, which is continued into adolescence.

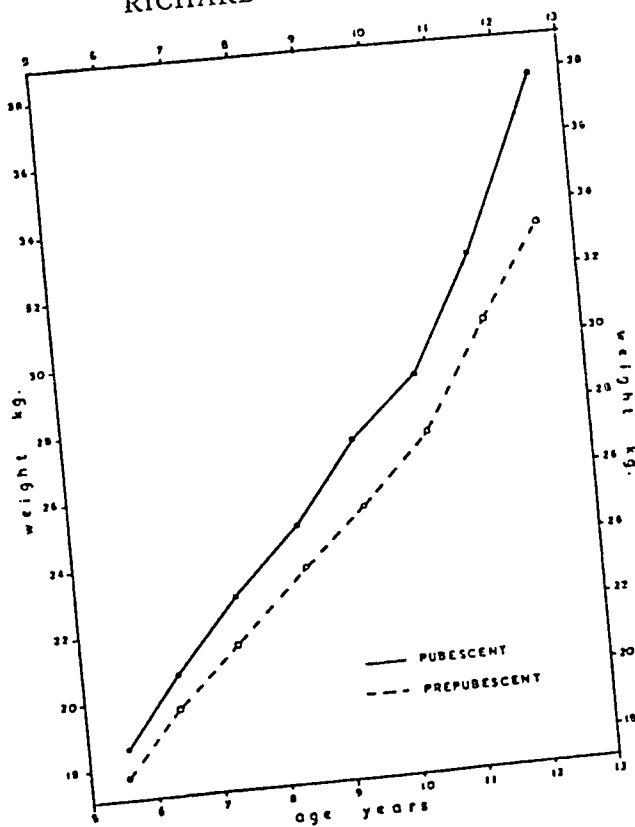


Fig. 10

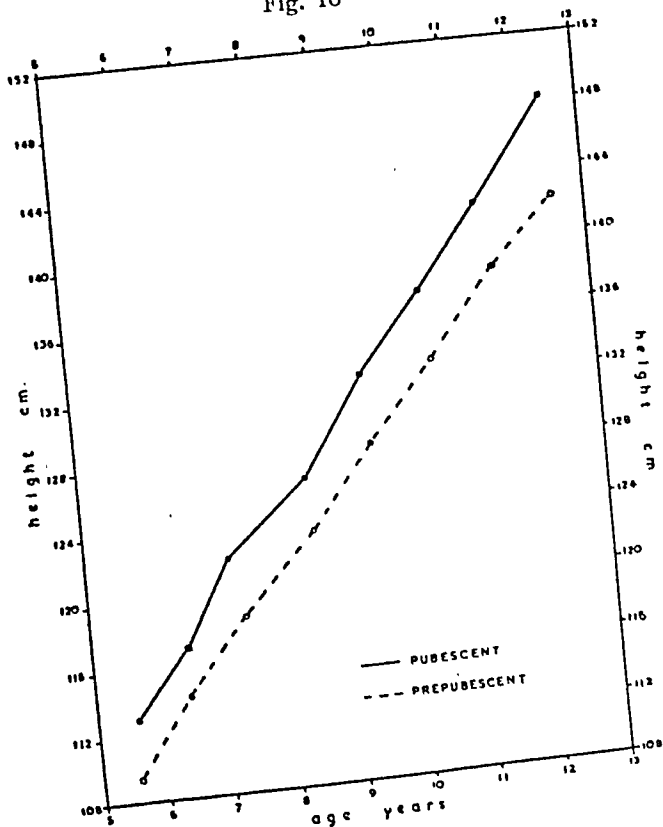
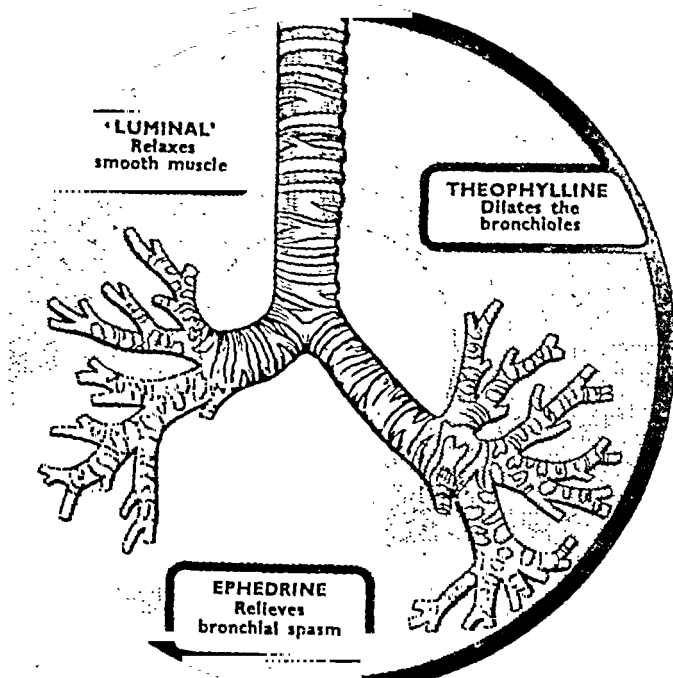


Fig. 11

FIGS. 10 and 11.—Comparison of mean height and mean weight curves of boys graded as pubescent (unbroken line) and non-pubescent (prepubescent) (unbroken line) when examined at age of 12 to 13 years (school A).

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### Calcium

An aid to formation of foetal skeleton and enrichment of breast milk.

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Although the amount of clinical material on which this study is based is relatively small, it does suggest that boys reaching puberty late are likely to be, on the average, smaller and lighter than their earlier maturing contemporaries, not only at the time of puberty but also throughout childhood. This does not of course imply that they will be smaller in adult life. In fact, in girls it has been repeatedly

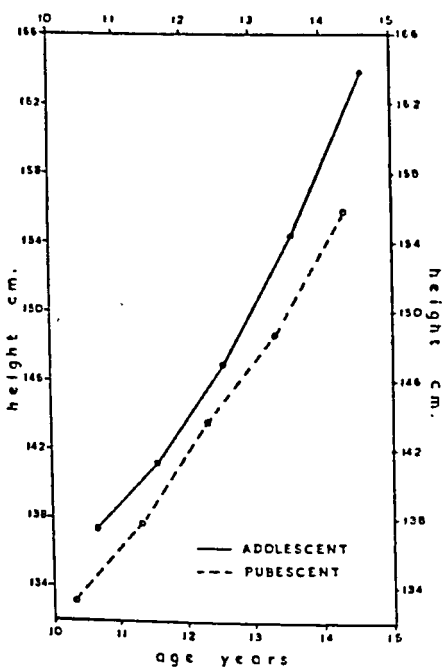


Fig. 12

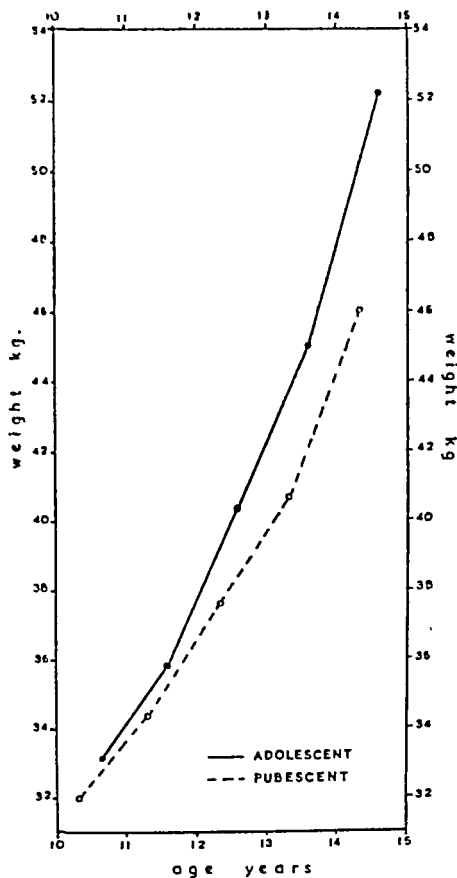


Fig. 13

FIGS. 12 and 13.—Comparison of mean height and mean weight curves of boys graded as adolescent (unbroken line) and pubescent (broken line) when examined at age of 14 to 15 years (school B).

shown (Stone and Barker, 1937; Simmons and Greulich, 1943) that those in whom the menarché occurs late tend ultimately to be taller than those who mature early, since growth continues over a longer period.

In the case of boys, accurate information with regard both to puberty growth and the relationship of early or late maturity to adult height is remarkably scanty. The reason for this has already been

mentioned, namely, the absence of a clearly-defined point such as the onset of menstruation, which can be determined retrospectively. By applying some such rough system of maturity-grading as I have outlined in the routine medical examination of schoolboys and boys in employment, it should, however, be possible to accumulate data on a large scale which would help to clarify the problems of growth in later childhood and adolescence. Even a more general recognition of the physiological range of age of onset of puberty would avoid many normal boys receiving endocrine therapy unnecessarily. This is particularly true of fat boys, who are far too frequently diagnosed as suffering from adiposogenital dystrophy, when the obesity is primarily exogenous and when puberty will occur normally without adventitious aid.

In conclusion I would emphasise again the very limited value of composite growth curves or tables of mean height and weight in relation to age in assessing the individual child. Unless the standard deviation is known for each point on the curve, no indication whatever is given of the range of normality in the groups of children in whom the measurements were obtained, and in the simple height and weight curves of the type I have illustrated, no true allowance can be made for the individual body-build. Various attempts have been made to overcome these difficulties. Thus the widely-used Baldwin-Wood Tables (1923) show the expected weight for height (over a range of 12 or more inches) in each year period for both sexes. More recently, an elaborate "Grid" for evaluating physical fitness in terms of physique (body build), developmental level, and basal metabolism has been devised by Wetzel (1943), which has considerable advantages in following the progress of the individual child. What I have attempted to illustrate is the importance of maturity rather than chronological age in assessing particularly the older child. Whilst puberty is the most dramatic and easily recognised phase of development in the child's life, it should be regarded as only one stage of maturity, each phase of childhood having its characteristic growth pattern. If the effect of maturity on growth is ignored, and children classified purely on chronological age, as is generally the case in our educational system, we have the anomaly that boys will start employment in such widely different stages of physical development that legislation for their protection in industry is largely futile. It is only necessary to compare two boys of 15, one who has not reached puberty and one who has reached late adolescence, to realise that lifting a given weight might be beyond the capacity of one and child's play to the other. The raising of the school leaving age should, however, have the great advantage of throwing a much smaller proportion of immature boys on to the labour market. It is to be hoped that the Education Authorities, to whom this mixed group of mature and immature boys will be handed back, will have the vision to deal with them on the basis of individual development rather than as yet another year-age group.

ACKNOWLEDGMENTS.—Figs. 4 and 5 are reproduced from *Child Health and Development* by courtesy of the publishers, Messrs J. & A. Churchill, and Figs. 1 to 3 and 10 to 13 from the *Archives of Disease in Childhood*.

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# THE CHEMOTHERAPY OF BENIGN TERTIAN MALARIA \*

By JAMES INNES, M.D., F.R.C.P.(Ed.)

Instructor in Medicine, Edinburgh Post-Graduate Board for Medicine

THE work on which this lecture is based was carried out in an Army Malaria Research Team between June 1944 and December 1946. This Unit was formed in the Mediterranean theatre of war and was attached to General Hospitals in Algeria and in Rome and later to the Military Hospital at Woolwich, London. The investigations were planned within the programme of malaria research directed by the Malaria Committee of the Medical Research Council and were intended to provide an opportunity for the study of antimalarial compounds in the treatment of malaria cases under active Service conditions. In addition the Unit acted as a centre where cases of recurrent malaria could be sent for special treatment. The cases treated at Woolwich were mostly returned prisoners-of-war from the Far East.

By the time that the Unit started work, the number of malaria casualties amongst troops in the Mediterranean theatre had diminished very considerably from the alarming figures experienced during the Summer campaign of 1943. The active field of operations had moved northward in Italy into less malarious areas and anti-malaria measures against mosquitoes and in the form of suppressive Mepacrine were much better observed. The total number of malaria cases handled by the team of four workers was only 700 of which the great majority were benign tertian infections. This represents a very small number of cases compared with those reported by therapy research teams in other theatres during the recent war or by previous workers carrying out large-scale therapeutic trials in India; and it was soon obvious that no conclusive comparison of the value of different drugs and treatment regimes could be based on the results of such a limited investigation. Accordingly it was decided to make the best use of the clinical material available by concentrating on a detailed laboratory study on the parasitological findings during therapy with various antimalarials in the hope that such observations might throw some light on the broader problems of malaria treatment. It is with this parasitological aspect of benign tertian chemotherapy that this lecture is mainly concerned.

It is convenient at the start to recall briefly the life-cycle of the parasite of Benign Tertian malaria in the human subject and to indicate in what way the unaided natural immunity defences of the body can modify this cycle as resistance to the infection is acquired.

\* A Honyman Gillespie Lecture delivered at Edinburgh Royal Infirmary on 15th May 1947.

The parasite *Plasmodium vivax* is injected into the human skin from the salivary glands of an infected mosquito in the form of a minute falciform organism known as a sporozoite. In spite of a great deal of investigation, the exact fate of the sporozoite in the body is not yet known but there is a lapse of from 10 to 14 days before parasites become demonstrable in the blood stream and the clinical manifestations of the infection occur. Many authorities believe that during this latent or incubation period, the parasite establishes itself in the reticulo-endothelial system of the host and that the asexual cycles which subsequently occur in the peripheral blood stream are initiated by these extra-erythrocytic forms. No one has yet been able to demonstrate such tissue forms of the parasite in human beings, although the postulation of their existence seems both logical and convenient as it affords an easy explanation for the occurrence of malaria relapses at long intervals after the blood stream has been cleared of parasites by therapeutic means. The tissue forms are believed to become well entrenched and to be little affected by drugs which terminate a blood stream invasion rather than produce a radical cure.

The forms and phases of the asexual cycle of *Plasmodium vivax* have long been studied in detail and can be found pictured in many textbooks. In Romanowsky-stained blood films the parasite in its youngest form, the trophozoite, is seen in a red blood cell as a small, thick, signet ring of blue-staining cytoplasm with a bright cherry-red spot of chromatin as a nucleus. The parasite rapidly enlarges to a more perfect oval ring and then becomes actively amoeboid as its name "vivax" implies. The growth of the parasite and its thrashing movements result in a considerable enlargement of the affected red cell which becomes paler in its staining qualities and shows numerous dots, known as Schüffner's dots, in its envelope. The amoeboid activity of the parasite gradually becomes more sluggish and vacuoles appear in its cytoplasm. Coincident with the growth of the parasite, which now almost fills the red cell, the chromatin nucleus enlarges and prepares to divide. Division of the nucleus is called schizogony, and in the strain of Benign Tertian parasite encountered in the Central Mediterranean, this results in the formation of 16 small nuclei around which the cytoplasm of the parent organism divides up to form 16 parasites of the next generation. Rupture of the red cell liberates the 16 little merozoites each of which then enters a fresh red cell and starts another asexual cycle. The complete asexual cycle, from the time of the youngest trophozoite to the liberation of the merozoites by the bursting of the merocyte, occupies 48 hours. Of this time the growth of the trophozoite from a small ring form to full maturity takes 36 hours and the stages of nuclear division or schizogony last 12 hours. The final rosette form of a merocyte lasts only a few minutes before bursting and the liberated merozoites are supposed to enter new red cells almost immediately. The disruption of the merocyte also liberates into the blood stream a quantity of malarial pigment

which has collected within the parasite cytoplasm. This golden-brown pigment begins to form in the cytoplasm of growing amœboid trophozoites, becoming diffusely scattered throughout later forms and collecting into a small granular mass during the schizont stages. It is believed that this liberation of the pigment, possibly with other foreign proteins, causes the pyrexial reaction which characterises the clinical condition at 48-hour intervals.

In all cases studied an attempt was made to record the actual number of malaria parasites in the peripheral blood at regular intervals during treatment. Thick blood films were used and the parasites were counted in proportion to the leucocytes and their number per cu.mm. worked out after estimation of the white blood cell count. A modification of Field's staining method was elaborated whereby very thick blood films could be de hæmoglobinised so enabling small numbers of parasites to be easily counted. (J. C. B. Fenton and J. Innes, *Trans. Roy. Soc. Trop. Med. Hyg.*, 39, 1, 87-90.) Parasite counts were done first at 12-hourly intervals, but this routine was altered in most cases when it became apparent that the rate of diminution of parasites during therapy was such that adequate data could be obtained from counts done at intervals of 24 hours.

In addition to recording the number of parasites present per cu.mm. of blood, the stages of development of the parasite asexual cycle represented by each count was noted. By such differential counts it was possible to study the effects of a drug on the phases of the parasite cycle as well as observing the quantitative clearance rate of parasitæmia.

On first thoughts the whole question of parasite counts in active cases of malaria might appear to be fraught with so many factors of variation that little information of value could be obtained from such a study. The possibility of several asexual cycles running concurrently in the same patient with each cycle multiplying itself 16 times each 48 hours, conjures up a picture of great confusion in assessing stages of parasite development and of astronomical figures in enumeration. It was soon found, however, that such difficulties do not exist in practice in uncomplicated B.T. infections, and the following general observations, made in untreated cases, are of interest and importance before considering the question of the action of antimalarial drugs.

In the majority of cases most of the parasites were found to be at the same stage of development at any one time. This meant that the parasite picture was dominated by one recurring asexual cycle with other cycles suppressed to an almost negligible minority. These cases accordingly showed the characteristic tertian fever but in other cases the occurrence of quotidian fever was clearly the result of more than one parasite cycle running at different stages. In these, however, two cycles were usually present and were quite easy to distinguish. More complicated parasite cycle patterns were most uncommon.

The degree of parasitæmia in cases with fresh B.T. infections was found in general to be very much less than that in relapse B.T. infections.

In the fresh cases parasite counts before treatment usually ranged from a few hundred to 2000 parasites per cu.mm., in contrast to counts of between 5000 and 10,000 per cu.mm. frequently found in recurrent infections. This difference is not surprising when it is considered that in subjects not previously infected, a relatively small number of parasites in the blood stream may be sufficient to produce the clinical features of the disease, whereas in relapse cases a degree of immunity has been acquired which raises the parasite threshold required to cause clinical manifestations.

In this connection it was found interesting to correlate the asexual parasite count estimated when the diagnosis of malaria was first established by blood examination, with the duration of antecedent symptoms described by the patient. It was evident that in relapse infections a comparatively high initial asexual parasite count was frequently found following a short period of premonitory symptoms, whereas in fresh infections a low initial parasitæmia was often present after a much longer period of clinical manifestations. A simple mathematical expression was devised to express this parasite-symptom correlation and was termed the "Immunity Factor" ("I.F."), which is obtained as follows:—

$$\text{I.F.} = \frac{\text{Initial asexual parasite count per cu. mm.}}{\text{Days of symptoms} \times 100}$$

*Examples—*

*Fresh Case.* Initial count = 800 per cu.mm.

Days of symptoms = 4.

$$\text{I.F.} = \frac{800}{4 \times 100} = 2.0.$$

*Relapse Case.* Initial count = 7000 per cu.mm.

Days of symptoms = 2.

$$\text{I.F.} = \frac{7000}{2 \times 100} = 35.0.$$

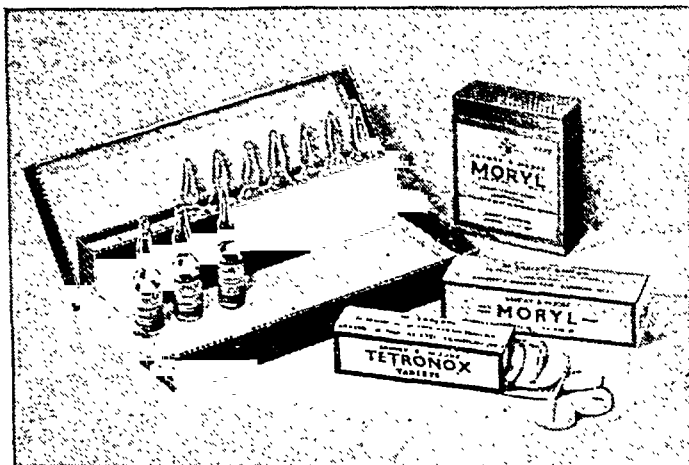
In a series of 156 fresh infections and of 254 relapse cases of B.T. malaria, it was found that the great majority of the fresh cases had factors of less than 15, while in nearly all of the relapse cases the factor was greater than 25. This calculation of an immunity factor is of academic interest rather than practical importance. It is a measure of the extent of peripheral asexual parasitæmia that the individual is able to withstand before feeling acutely ill and thus is possibly an expression of the degree of acquired immunity. It was found to provide useful evidence in some cases where there was doubt as to whether the infection was fresh or relapse, and it was noticed that in relapse cases the highest factors were obtained during the months when 0.1 gm. of suppressive Mepacrine was a routine daily issue. This

would suggest that relapses occurring in subjects taking suppressive Mepacrine tend to develop with great suddenness of onset and with a heavy parasitæmia, and it was further noted throughout this work that heavy B.T. blood infections were very uncommon in patients who had taken little or no suppressive Mepacrine.

Another question that must be considered before repeated parasite counts can be used as an indication of the response to therapy in malaria cases, is the variation likely to be found in the number of parasites in the peripheral blood in untreated infections. Preliminary work in which counts were done at frequent intervals throughout the day soon showed that apart from the time of the bursting merocyte stage, the number of asexual parasites remained remarkably constant in any one case of B.T. malaria and that changes in the count were so gradual that estimations done at 24-hour intervals could provide adequate information. This is in great contrast to Malignant Tertian infections where dramatic changes in the asexual parasite count in the peripheral blood were found to occur within a period of a very few hours, and where an assessment of therapy by such methods is in consequence much more difficult.

In untreated fresh B.T. infections, parasite counts showed a gradually increasing asexual parasitæmia coincident with the increasing severity of clinical manifestations. The rise in parasite numbers, however, was usually slow, so that several complete 48-hour cycles would be required to step up the parasitæmia from a few hundred parasites per cu.mm. to two or three thousand. In relapse infections, asexual parasite counts above 20,000 per cu.mm. were exceptional, and the very slight variation found in the number of parasites over periods of several days in untreated cases was especially noticeable. In many cases the counts either remained constant or even decreased slowly, indicating that spontaneous recovery was taking place. Spontaneous recovery of B.T. relapses is, of course, quite common in patients receiving ordinary rest and attention in bed without specific therapy; and cases that appeared to be about to cure themselves had to be excluded for the purposes of a therapeutic trial. It is interesting to remember that each B.T. asexual parasite is capable of producing 16 parasites of the next generation, so that theoretically the parasitæmia should multiply by 16 times each 48 hours. The fact that such does not occur in practice, and that the counts can remain almost constant, means that the immunity defences of the host can destroy unaided fifteen-sixteenths of the parasites. Any drug therefore, which can retard the development of the asexual cycle, or can destroy even a small proportion of the parasites, should enable the body to wipe out the parasitæmia. The chemotherapy of B.T. malaria provides a good example of the relatively small rôle played by a drug in assisting the body to combat an infection.

The antimalarial drugs used in the therapeutic trial were Quinine, Mepacrine, Pamaquin and Paludrine. Various treatment courses



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employing different dosages and combinations of these were administered and the general results obtained can be summarised together with some of the points observed regarding the mode of action of the drugs on the parasites.

In B.T. fresh infections a comparison was made between therapy courses in which for the first 3 days of treatment, Quinine alone (10 gr. t.i.d.), or Mepacrine in low (0.2 gm. t.i.d. for 24 hours then 0.1 gm. t.i.d.), or heavy, (0.2 gm. q.i.d. for 48 hours then 0.1 gm. t.i.d.), dosage, was given orally. It was found that in all cases the average duration of asexual parasitæmia from the start of treatment was less than 2.5 days. Mepacrine produced a slightly more rapid clearance of parasites than Quinine, although from the point of view of relief of symptoms and reduction of pyrexia, Quinine proved to be more satisfactory.

In B.T. relapse infections it was found that the average duration of treatment required to clear asexual parasites from the peripheral blood, was less than 2 days on therapy courses consisting of Quinine plus Pamaquin (10 gr. plus 0.01 gm. t.i.d.), heavy Mepacrine (0.2 gm. q.i.d.), or Paludrine (250 mgm. t.i.d.). Using Pamaquin alone, in doses of 0.01 gm. t.i.d., the average duration of asexual parasitæmia was 3.1 days. A point of interest in these relapse cases was that the rate of clearance of parasites seemed to depend little on the height of the initial count, since cases starting with from 10,000 to 15,000 parasites per cu.mm. were cleared as quickly as those with counts between 1000 and 5000 per cu.mm. After 36 hours of treatment the average counts of all cases would appear to fall within a close range of one another, which indicates that very rapid clearance of asexual forms occurs early in those cases with a heavy initial parasitæmia.

Four changes were frequently detected in the asexual cycle of B.T. parasites, apparently resulting from the action of these anti-malarial drugs. The first change consisted in a general slowing down of the rate of development and maturation of the various parasite stages, so that the early and late trophozoites and the schizont stages succeeded one another in a much more leisurely or retarded cycle than normal. In the growing trophozoites two changes were seen, consisting of a tendency to collapse of the large ring and vacuolated amoeboid forms, and a bunching together of the malarial pigment which is usually scattered diffusely throughout the cytoplasm of the later trophozoites. The fourth and most important change implied the actual destruction of one or more of the parasite stages in the asexual cycle.

The four drugs used in this trial all followed in general this scheme of fourfold attack upon the B.T. asexual parasite. There were, however, certain differences between them in the varying intensity of their detailed actions and especially in the manner in which they selected different parasite stages on which to exert their maximum destructive effect. These differences are best dealt with by giving, in



the case of each drug, a short summary of the findings which suggest its probable mode of action.

*Quinine*.—Quinine seemed to be the most rapid of the antimalarials in the speed of initial action and it produced, after about 12 hours, the most powerful inhibiting effect on the general development of the parasite asexual cycle. It differed from the other drugs in causing no obvious collapse of the amœboid trophozoites and no bunching of malarial pigment. The maximum killing effect on the parasites appeared to be exerted on the merozoites, liberated by the bursting of the mature merocyte, and on the youngest trophozoites just establishing themselves in fresh red blood corpuscles.

*Mepacrine*.—Mepacrine was also speedy in its rate of initial action and produced, in about 18 hours, a powerful inhibition of parasite maturation. It caused very definite collapse of amœboid trophozoites and also marked bunching of parasite pigment. Early, intermediate and late schizonts and merocytes were all destroyed by Mepacrine, which actually proved to be the most rapid drug of the four in the clearance of asexual parasitæmia.

*Pamaquin*.—Pamaquin was the slowest of the drugs in producing any noticeable effects on the parasites and more than 24 hours were required before any retardation of the asexual cycle was evident. This slow start has no doubt contributed largely to the view that Pamaquin has little direct action on B.T. asexual parasites. When the Pamaquin inhibition did begin, it resulted in marked slowing of the maturation of growing trophozoites, as seen with Quinine and Mepacrine, but unlike the latter drugs it caused very little tendency to an arrest of parasite development at the very late trophozoite or pre-schizont stage. The trophozoites therefore were subjected to a general retardation of growth but appeared to undergo nuclear segmentation relatively unimpeded and reached the later stages of schizonts before they were destroyed. The maximum destructive effect of Pamaquin seemed to be exerted on late schizonts and merocytes, and those parasites that survived this phase and escaped from the bursting merocytes to start afresh as young trophozoites, usually continued development until the late schizont stages of the next asexual cycle before they were overcome. This powerful schizonticidal action of Pamaquin does not seem to be widely recognised. It appears all the more striking when it is remembered that the daily dosage of the drug (30 mgm.), is 20 to 30 times smaller than the dosage of Mepacrine necessary to produce an equivalent destruction of schizonts.

Pamaquin was also observed to cause collapse of the amœboid forms of trophozoites though this change occurred later and less intensely than with Mepacrine. Conglomeration of malarial pigment in late amœboid trophozoites was frequently seen in cases treated with Pamaquin alone and the bunched-up pigment was often actually extruded from the parasite cell. When such liberation of pigment occurred almost simultaneously from large numbers of late trophozoites,

it was noticed to coincide clinically with a typical rigor and attack of malaria fever. In cases where this effect was observed, the clinical paroxysm took place at a time when the asexual parasites were still at the stage of young schizonts, so that it seems that Pamaquin therapy can in these circumstances bring about a pyrexia that is premature according to the usual timing of the B.T. parasite cycle.

*Paludrine*.—This new antimalarial was given in varying doses to a number of B.T. cases, mostly relapse infections. The effects on the asexual parasites were noted mainly in cases receiving oral dosage of 250 mgm. t.i.d.

Paludrine was slower than Quinine or Mepacrine in producing visible effects on parasite development. It caused a distinct retardation in the growth of young trophozoites, but appeared rather less powerful in this respect than the other three drugs investigated. Its maximum destructive effect was exerted against earlier forms of schizonts than was seen with any of the other antimalarials, all of which attacked late schizonts and merocytes. Collapse of the amœboid trophozoites occurred, but this was a late effect and was often incomplete. The pigment present in mature trophozoites became coarsely granular but showed no definite bunching or extrusion. The most striking and distinctive effect of Paludrine on the asexual parasites occurred in the form of its interference with the division of the chromatin nucleus. Differentiation of the chromatin of the segmenting trophozoite into numerous rod-like structures was seen to take place in the normal manner, but instead of these re-grouping to form two distinct nuclei, the chromatin remained in this differentiated phase, apparently inhibited from further development. Parasite forms showing this unusual state of nuclear chromatin arrest were produced, sometimes in large numbers, and persisted for long past the time when they should normally have undergone complete schizogony. These were not uncommonly the last forms of asexual parasites to be found in the peripheral blood during Paludrine therapy, and their close similarity in appearance to female B.T. gametocytes in thick blood films often proved troublesome in differential parasite counts, especially as the latter were themselves noted to be very persistent in treatment with this drug.

A general effect, noted late in Paludrine therapy, was that asexual parasites in various stages of degeneration were found, with fading cytoplasmic staining and indistinct chromatin. These degenerate forms occurred at any phase of the developmental cycle and were more commonly seen with this drug than with Quinine, Mepacrine or Pamaquin. Parasites affected in this way seemed to fade quietly out of the blood picture without showing any gross morphological changes.

It will be seen that all of the four drugs studied act most destructively on the schizont stages of B.T. asexual parasites, and that they also

cause, in varying degree, a retardation of the rate of development of young trophozoites. If this inhibiting action is marked, as with Mepacrine, there is a tendency for the growing parasites to be arrested in their development before they have matured sufficiently to be affected by the schizonticidal action of the drug. This results in a relatively long persistence of parasites, mostly in an arrested pre-schizont stage, and is likely to occur in cases where therapy is started at a time when the majority of parasites are middle-stage growing trophozoites. Differential parasite counts showed that such inhibited pre-schizonts were found most frequently during treatment with Mepacrine and Quinine, and an experiment was designed whereby the schizonticidal action of Mepacrine could be observed on parasites that had not previously been influenced by the inhibitive effect.

For this experiment two cases, with a moderately heavy B.T. infection with tertian fever, were left untreated until the parasites had developed to the stage when nuclear splitting was just about to occur. They were then given an intramuscular injection of Mepacrine 0.2 gm. and no further specific treatment was given during the following 24 hours. Blood films were examined at frequent intervals after the injection and it was found that a most striking clearance of asexual parasites resulted. In one of the cases, a parasite count of 14,000 per cu.mm. was reduced to 50 per cu.mm. in 24 hours, and in the other case the initial count of 4200 per cu.mm. was completely cleared within 8 hours. It was noticed that the patients experienced an unusually sharp clinical paroxysm during this rapid clearance, and a further study was made of this interesting finding in a series of 27 cases of fresh and relapse infections injected in the same manner.

Following the injection of Mepacrine at the pre-schizont parasite stage, there is a delay of 2 to 4 hours before any morphological changes due to the drug are seen in the parasites. The first change is then the collection together of the malarial pigment, but the parasites continue to develop without apparent arrest and there is little or no alteration in the total count for 5 to 8 hours. By this time the parasites have nearly all become young schizonts and they have begun to extrude their bunched-up malarial pigment into the circulation. It is this extrusion of pigment that results in the occurrence of a clinical malarial paroxysm such as is usually seen at sporulation time, but the symptoms of the premature pyrexial reaction tend to be more severe, with vomiting and muscular cramps. The sudden fall in the parasite count occurs between 4 and 12 hours after the injection and at a time when the parasites have developed to the stages of middle and late schizonts. It appears that the younger schizonts are only slightly affected by the drug. In 8 of the cases, plasma Mepacrine levels were estimated following the injection. It was noticed that the maximum clearance of parasites corresponded in time with the fall of the initially high plasma Mepacrine level. The latter, according to workers who have studied the distribution of Mepacrine in the

blood and tissues, is brought about by the transference of the drug from the plasma to the circulating red and white blood corpuscles and to the tissues. It would appear likely therefore, that this transfer of the drug to the parasitised red cells is connected with the clearance of parasites as observed.

This experiment with injected Mepacrine, while having little or no practical bearing on the treatment of malaria cases, serves to shed light on the mode of action of the drug and shows how, in ordinary circumstances, its effect in retarding trophozoite maturation may delay its more powerful lethal effect on the schizont stages. When administered to act unimpeded on the most susceptible phases of the parasite cycle, a single injection of 0.2 gm. of Mepacrine was shown to be capable of clearing from the blood stream in a few hours, the vast number of parasites represented by a count of nearly 20,000 per cu.mm. It is in this demonstration of the potency of the drug as a schizonticide, that the main interest and value of the injection experiment lie.

In the treatment of B.T. malaria infections the clearance of gametocytes, the sexual forms of the parasite, is of much less importance or interest than the clearance of asexual parasitaemia. There is no evidence that the gametocytes play any part in the course of the disease in the human subject, and they are believed to represent only the means whereby the parasites allow for the natural continuation of their species in providing sexual forms capable of reproduction in a suitable mosquito sucking blood from the human host. Since gametocytes appear, often in large numbers, in the human blood stream during active infections, their recognition and enumeration become essential when parasite counts are done to assess the anti-malarial activity of drugs. The observations made in regard to the clearance of gametocytes may be summarised briefly.

In fresh and relapse B.T. infections, Quinine and Quinine plus Pamaquin courses were both more effective in clearing gametocytes from the blood than Mepacrine therapy. In general, gametocytes were slower in disappearing than asexual forms, and in many cases, especially in those receiving low Mepacrine dosage, they continued to appear in fresh showers for several days after the asexual parasites had been cleared. This was particularly noticeable with the female gametocyte which is the largest form of B.T. parasite found in the blood. Pamaquin was found to be the one drug capable of clearing gametocytes in a time as short or less than that required to get rid of the asexual parasites, and it proved to be easily the most powerful gametocide. Paludrine, in contrast, was in all cases the weakest anti-malarial tested in respect of gametocyte clearance. In cases treated with 250 mgm. t.i.d. and with larger doses, it was noticed that female gametocytes were able to persist in the blood for up to one week after the start of treatment.

In any therapeutic trial in malaria a careful follow-up of cases over an adequate period of treatment is of fundamental importance. In B.T. malaria, where there is a natural tendency for relapses to occur after an interval of several months, the selection of too short a follow-up period may give an entirely erroneous impression of the value of a form of treatment in preventing recurrences. Furthermore, in comparing the late results of therapy with Mepacrine, and Quinine plus Pamaquin treatment, it must be remembered that after the latter drugs, the relapse is frequently in the form of an early recrudescence of the infection, which would give an undue advantage in favour of the Mepacrine if a short follow-up time were adopted. In the therapeutic trial reported here, six months was selected as the minimum follow-up period, and many cases were observed for longer. It was possible to follow adequately a total of only 450 cases but the general results obtained are worth reporting.

In fresh B.T. infections no significant difference in relapse rate was found after treatment consisting of courses containing Quinine and Mepacrine, or Mepacrine alone, in high or low dosage. In the treatment of relapse infections, a 10-day course of Quinine plus Pamaquin proved significantly more effective than heavy Mepacrine dosage (4.6 gm. in 12 days), in preventing relapses. The Quinine plus Pamaquin doses appeared to produce a radical cure in 8 or 9 out of every 10 cases treated. A similar low relapse rate was found in cases of B.T. malaria, acquired in the Far East, and treated with a 10-day course of Paludrine 250 mgm. plus Pamaquin 0.01 gm. t.i.d., but the latter dosage regime is not recommended in view of the frequent toxic manifestations it caused. The relapse incidence after treatment with Paludrine alone was as high as with Quinine and Mepacrine therapy. In over 200 cases who were given Pamaquin at some stage of treatment, the relapse rate was statistically significantly less than in a similar number of cases to whom other antimalarials, but no Pamaquin, was given.

By far the most striking follow-up was in a series of 50 cases treated for multiple B.T. relapses with an intermittent dosage of Quinine plus Pamaquin over a period of 30 days. In these not a single case of relapse was reported. The reasons for the unique success of this treatment are not easy to postulate, but as early recrudescences are the common form of relapse after Quinine and Pamaquin, it is possible that an intermittent course would be more successful than a continuous course in dealing with an infection which tended to remain inhibited in some latent and resistant form during the administration of antimalarial drugs. It should be noted in this connection, that both Quinine and Pamaquin are excreted fairly quickly from the body and any such inhibition exerted by them would thus soon be removed during the intervals in the treatment course, whereas with a slowly excreted drug like Mepacrine, any action on latent parasite forms would tend to be much more sustained.

In conclusion it is well to consider the criteria on which the therapeutic assessment of an antimalarial compound should be based and to place in their proper perspective the value of detailed parasite studies in such work. The ideal antimalarial drug is one which will, in non-toxic doses, produce a rapid clinical cure of the blood stream infection and at the same time eradicate the tissue forms of the causal parasite, so effecting a radical cure with complete freedom from relapses. In Malignant Tertian malaria Paludrine would seem to fulfil these criteria and it is undoubtedly the greatest advance in malaria therapy since Quinine was first used. As a drug that kills the tissue forms, it is also the ideal causal prophylactic, and taken in small and safe doses over a long period, it can prevent sporozoites from establishing themselves in the body and setting up a bloodstream infection. The world-wide problem of M.T. malaria would now seem to be only one of the availability and distribution of large enough supplies of this drug.

In Benign Tertian malaria the ideal drug has so far not been found and this infection with its tendency to relapses continues as one of the great "nuisance" diseases of mankind. In the search for a suitable drug, parasite studies afford not only a means of measuring the rate of clearance of asexual parasitaemia, but provide an essential spotlight on the mode of action of a compound on the causal parasite, with which many of the clinical effects can be correlated. As an example of how it is possible to forecast the value of a drug from observing its action on parasites, it could be reasonably expected that Paludrine would produce no striking cure of active B.T. malaria, as soon as it was evident that its main effect on the asexual cycle was to attack the schizont stages and to inhibit the trophozoites in much the same manner as Quinine, Mepacrine and Pamaquin. No compound yet tried has been found to destroy specifically the growing trophozoites of B.T. malaria, and it would indeed be interesting to observe the curative value of such a drug, which might well be expected to effect a new type of therapeutic response in this condition.

The recent war has shown once again the value of directed and concerted effort in overcoming problems, and in few fields has this yielded more fruitful results than in the attack on malaria. It is to be hoped that the close liaison established in this work between the clinician, the parasitologist, the synthetic chemist and the biochemist will continue to develop so that before long we may see *Plasmodium vivax* written off the list of the parasites that lay low the human race.

## THE USE OF ERGOT FOR INDUCTION OF LABOUR AND FOR THE THIRD STAGE OF LABOUR \*

By W. D. A. CALLAM, M.B., F.R.C.S.Ed., M.R.C.O.G.

MR PRESIDENT, FELLOWS, LADIES AND GENTLEMEN,—To-night I would like to say a few words about the use of Ergot for Induction of Labour and the Third Stage of Labour.

I know full well that this is an extremely controversial subject, and that the use of ergot prior to the delivery of the placenta has been frowned on for many generations, but I hope that I will be able to convince you that there is a place for its use in these conditions.

Before embarking on the more practical side of the subject perhaps a few words regarding its history would be of interest. For at least four centuries powdered ergot (the nail-like growths in diseased rye) has been used to hasten labour that is lingering, and a description of the early use of the drug has been expounded in Barger's *Ergot and Ergotism*.<sup>1</sup>

Early in the history of its medical use there were many foetal and maternal disasters, and Hosack<sup>2</sup> in 1822 said, "Ergot has been called Pulvis ad Partum: as regards the child it may, with almost equal truth, be denominated Pulvis ad Mortem!"

More recently many alkaloids have been isolated from ergot, and all appear to be built on the basic nucleus of lysergic acid. Only three have really found their way into clinical medicine, Ergotoxine (Carr and Barger, 1906),<sup>3</sup> Ergotamine (Stoll, 1920),<sup>4</sup> and Ergometrine (first described in 1935 by Dudley and Chassar Moir<sup>5</sup>). The latter is also known under other names: it is called Ergonovine by the Council of Pharmacy and Chemistry of America, Ergotocin by Kharasch and Legault,<sup>6</sup> Ergosterine by Thompson,<sup>7</sup> and Ergobasine by Stoll and Buckhardt.<sup>8</sup>

To Dudley and Chassar Moir<sup>5</sup> goes the first credit of description of this alkaloid, but there is no doubt that many investigations were being carried out in 1935 on its action. At one time it was thought that Ergometrine, Ergonovine, etc., were all different chemically, but further work showed that the substances were identical.

Ergotamine and Ergotoxine have been to a great extent discarded for clinical use, because they are so slow in their initial action, but Ergometrine, which has a smaller molecule, is much more rapid in its onset, and therefore more suitable for use in labour.

Originally the firm of Sandoz of Basle experimented on Ergobasine as described by Stoll and Buckhardt,<sup>8</sup> and put it on the market under

\* Read at a Meeting of the Edinburgh Obstetrical Society, 13th February 1947.

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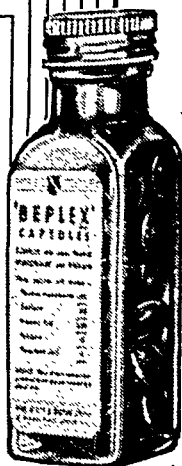
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the name of Basergin. Investigations by Rothlin<sup>9</sup> showed that it produced the characteristic ergot effect on the uterus with a rapid onset of action and of relatively short duration: he considered that it could be adapted for use in the first and second stage of labour, and that if given by mouth it would produce the required effect on the uterus, which was an additional advantage.

Following further research by chemically altering the Ergobasine molecule, a more suitable substance in methyl-ergobasin was found. Rothlin<sup>9</sup> considered that this new substance had twice the effect of the original Ergobasine.

This, therefore, is the substance produced semi-synthetically by Sandoz under the trade name of "Partergine," and which I have used for the induction of labour in my series of cases. A similar substance called Methergine has been produced in America, the main difference being that it is in stronger solution.

Partergine is prepared for oral administration, and each cubic centimetre of the solution contains 0.075 mgm. of methyl-ergobasine tartrate.

*Method.*—The method employed has been as follows:—

At 5 a.m. the patient is given one ounce of castor oil and this is followed one hour later by a warm soap and water enema. Commencing at 11 a.m.  $\frac{1}{2}$  c.c. of Partergine diluted in 10-15 c.c. of water is given orally, and this is repeated if required at half-hourly intervals for a further three doses. A similar course of Partergine is given on the two following days if labour has not become established.

It will be noted that the dose administered has been relatively small, but in view of the potential danger in the use of ergot, great caution has been observed. An additional safeguard might be to use a very small dose initially, in order to test the sensitivity of the uterus, but it was not employed in my series.

It is preferable to give the substance on an empty stomach, in order to ensure quicker and better absorption.

*Indications.*—The indications for induction of labour are both maternal and foetal, although naturally mainly the former: these include toxæmias of pregnancy, intra-uterine foetal death, premature rupture of the membranes, post-maturity and marked hydramnios.

It should not be employed in cases of cephalo-pelvic disproportion.

In my series there were 17 cases of toxæmia, three cases of premature rupture of the membranes with complete inertia, two apparently genuine cases of post-maturity, one case of hydramnios with twins, one of intra-uterine death, and lastly one of hydrocephalus (followed by perforation when the cervix was sufficiently dilated).

*Results.*—This method was employed in a series of 25 cases, and was successful in 20 of them (80 per cent.). If labour pains had not commenced within six hours of the last dose of Partergine, then induction of labour was considered to have been a failure.

In this series there were no cases prior to the thirty-sixth week.

*The Average Number of Doses required to Induce Labour*

	Number.	Average Number of Doses.
Total successful cases . . . . .	20	
Primigravidæ . . . . .	9	4.9
Multiparæ . . . . .	11	6.4
Primigravidæ with membranes unruptured . . . . .	9	4.9
Multiparæ with membranes unruptured . . . . .	8	6.9
Multiparæ with membranes ruptured . . . . .	3	5.3

In many cases more doses were given than was required for initial induction, but this was done to increase the strength and frequency of uterine contractions. There seemed to be no ill-effect from continuing its use until the patient was having pains every seven to ten minutes.

*Degree of Taking-up of Cervix.*—Of the nine primigravidæ successfully treated, the cervix was not taken up in five cases, and partially taken up in four, whilst there were eleven multiparæ with the cervix not taken up in three, partially taken up in seven, and completely in one case.

Among the failures there were three primigravidæ and two multiparæ with the cervix not taken up in three of them, and partially taken up in two.

*Maternal Effects.*—There appeared to be no untoward effect on the mother following induction with Partergine. Blood pressure, pulse, respirations were checked, and there was no appreciable change.

The oral administration did not cause any gastro-intestinal upset. There did not appear to be any change in the postpartum period either from the point of view of duration or blood loss.

The effect of Partergine on the patient was as follows: a complaint of backache and lower abdominal discomfort occurred more or less simultaneously, and very shortly afterwards definite contractions of the uterus could be felt on abdominal palpation. In no case was there any evidence of uterine tetany, although in one the uterus between contractions remained for a short time slightly more tense than usual; but this did not cause any ill-effect to either mother or child, and was never sufficient to cause any anxiety.

The length of labour appeared to be slightly shorter than normal.

*The Length of Labour in this Series*

	Number of Cases.	Average Hours in Labour.
Primigravidæ with unruptured membranes . . . . .	9	17 hrs. 4 mins.
Multiparæ . . . . .	11	9 " 6 "
With unruptured membranes . . . . .	8	8 " 45 "
With ruptured membranes . . . . .	3	9 " 46 "

*Effects of Fœtus.*—There did not appear to be any untoward effect on the fœtus in either the successful or the unsuccessful cases. Excluding the hydrocephalus which was perforated, there was in one

case a still-birth, but this was following a very difficult forceps delivery for arrest at the outlet in the occipito-posterior position. Post-mortem examination revealed that there was a massive intracranial hæmorrhage. The foetal heart had been quite normal prior to delivery. There were no neo-natal deaths.

In all cases the foetal heart was listened to carefully, and Partergine did not seem to cause any disturbance either to its rate or volume.

*Comments.*—I quite realise that it is impossible to be dogmatic in such a small series, but I would like to stress the following points:—

From the results it would appear that Partergine was as successful in the induction of labour as any of the other better known methods. It did not have any deleterious effect on mother or child: this preparation would therefore appear to be much safer than Ergometrine or Ergonovine as Wolf,<sup>10</sup> using the latter drug, had serious foetal complications.

This method certainly causes less physical disturbance to the patient, oral administration being preferable to injections or other surgical techniques.

As Partergine is an oxytocic drug, the same precautions must be taken as with any other drug that is sufficiently potent to cause strong uterine contractions. Theoretically, uterine tetany and rupture are possible, and that being so knowledge of an antidote might be helpful. Abarbanel<sup>11</sup> of Washington reports that the use of the magnesium ion brings about relaxation of the uterine muscle and relief from pain very rapidly. He advocates its use intravenously, injecting either 2 c.c. of a 50 per cent. solution of magnesium sulphate or 10 c.c. of a 20 per cent. solution of magnesium gluconate.

In comparing my results with those of Farber<sup>12</sup> of Philadelphia who used Methergine, which is a similar but stronger solution (0.25 mgm. per c.c.), it is noted that they are comparable with his first series of 11 cases, in which he had a 72.8 per cent. success without ill-effects. He did a further series using much bigger doses, the first nineteen of them being completely successful, and a further thirteen showed two failures.

That being so I would suggest that in view of the fact that there was no ill-effect on mother or child in either series, that Partergine should be given a further trial using larger and more repeated doses in the hope of obtaining a greater percentage of success. Cases would of course have to be watched most carefully for fear of complications.

#### THE USE OF INTRAVENOUS ERGOMETRINE AT THE END OF THE SECOND STAGE OF LABOUR

I think that most of you will agree that the third stage of labour is the most important phase of parturition. This short period may be packed with many dangers for the mother, and post-partum hæmorrhage contributes very appreciably to maternal mortality both

from blood loss and the danger of infection resulting from manipulations necessary to control bleeding.

During the last few years some new factors have entered into the conduct of labour, which have effected the course of the third stage. More patients are confined in hospitals and labour is often terminated in a primigravida by a low forceps and episiotomy instead of allowing unnecessary prolongation of the second stage. These necessitate the use of anæsthesia. Also analgesics are more frequently employed, which sometimes prevent the patient from co-operating in the second stage, thus resulting in an increasing operative delivery.

The three factors, analgesia, anæsthesia and operative delivery will naturally tend to interfere with the normal third stage, with the possibility of increasing complications in this stage. Other causes include prolonged difficult labour, placenta prævia, overdistension of the uterine cavity as in twins, hydramnios, etc.

Davis<sup>13</sup> of Chicago considers that the third stage consists of two distinct phases, namely separation and expulsion, and believes that no attempt should be made to initiate the latter until the former is completed. The first phase involves a slow separation of the placenta from the uterine wall. The placenta normally remains attached to the uterus until the expulsion of the fœtus. The sudden diminution in size of the uterine cavity causes a reduction in the surface area of the uterine wall to which the placenta is attached: the non-contractile placenta cannot alter its surface area, with the result that it either partially or completely separates from its attachment. Davis<sup>13</sup> considers that the speed with which the reduction of the uterine surface area is accomplished determines the completeness of the separation. Normally complete separation rarely takes place immediately, but a retro-placental clot forms, and some consider that that helps in the further separation of the placenta, although it does not appear to be absolutely necessary. Further contractions take place with more separation.

It seems therefore that placental separation depends on the contractility of the uterus, and I think that most of you will agree that there is more likelihood of greater blood loss the longer the third stage, and the less complete the separation.

If placental separation is due to the sudden reduction of the surface area of the placental site, then it is obvious that the more rapidly the reduction takes place, the more complete will be the separation.

Intramuscular Ergometrine and posterior pituitary extract have been used in the third stage, but their action compared with the intravenous therapy is relatively slow and probably only expels the already separated placenta into the non-contractile lower segment or vagina.

The intravenous administration of Ergometrine is followed by a sudden uterine contraction of maximum intensity and tone.

*Method.*—To accomplish this immediate contraction of the uterus

following the birth of the baby, I have used 0.125 mgm. Ergometrine intravenously after the birth of the anterior shoulder. The drug usually acts on the uterus within twenty to thirty seconds, and during this period the rest of the delivery of the child can be safely accomplished.

It is my opinion that the uterus contracts almost immediately, shearing the placenta completely from its attachment and pushing it into the lower uterine segment or vagina; in other words, it promotes and hastens the normal natural maternal mechanism. Following this, abdominal palpation will usually reveal a firm globular uterus sitting above an already separated placenta. The placenta should now be expressed manually with the aid of slight traction on the cord if necessary.

*Results.*—I have made use of this method in 100 cases, and an attempt has been made to make as careful observations of the third stage as possible. The Sisters in charge of the labour wards and the Residents have been most helpful in this matter.

On account of the shortage of staff it has not been possible to measure accurately the amount of blood loss, but a clinical estimation has been made, dividing it into three groups :—(1) Minimal, (2) average and (3) excessive post-partum hæmorrhage. Any blood loss over 300 c.c. would be considered as excessive, and under 100-150 c.c. as minimal.

The results have been highly satisfactory and in none of the series has there been an excessive hæmorrhage either in spontaneous or operative deliveries. It is considered that the blood loss has been minimal in approximately 75 per cent. of the cases.

*Types of Case in which Intravenous Ergometrine Used*

	Number of Cases.	Spontaneous Delivery.	Forceps.
Primigravidae . . .	72	55	17
Multiparæ . . . .	28	25	3

In the latter group there had been in three cases a history of manual removal of placenta, two of them being associated with profuse hæmorrhage. In all of these using this method the length of the third stage was extremely short and the loss minimal.

No attempt has been made to use this technique in breech deliveries, as it might lead to trouble in delivering the child.

*Length of the Third Stage.*—The length of the third stage has been shortened, and there appears to be a direct relationship between the blood loss and the length of the third stage.

In the majority of cases the separation of the placenta would appear to be almost instantaneous, with the result that it is ready to be expelled as soon as the baby has been attended to.

Thus the third stage rarely lasts longer than five minutes, and in

only 3 per cent. of cases was it longer than twenty minutes. In one case the placenta was retained and a manual removal was required.

The history of the labour in that case was as follows:—Patient was a primigravida, aged 33 years, who went into labour at the 42nd week—the head was high but there appeared to be no disproportion. The position was a left occipito-posterior and the labour was complicated in the first place by a primary uterine inertia. Progress was very slow, and eventually, after seventy hours of labour, a deep transverse arrest occurred, which necessitated manual rotation of the head and forceps delivery on account of marked maternal distress. 0.125 mgm. of Ergometrine was given intravenously after the birth of the anterior shoulder. Patient's condition following operation was poor, so expression of the placenta was not attempted, as there was no evidence of any third-stage hæmorrhage. Later examination revealed that the placenta was still *in utero* so, since her general condition had improved, one unsuccessful attempt at Crede's expression was tried. Further anæsthetic was then administered, and manual removal performed. The placenta was found to be quite separated from the uterine wall, but retained *in utero* by a contraction ring which nipped the placenta in its lower third. Removal of the placenta was easy and there was no bleeding. Unfortunately I was not present at this case, otherwise I would have liked to use intravenous magnesium to see if it would have relieved the uterine spasm. Abarbanel<sup>11</sup> considers this to be most effective in such cases. Possibly this case demonstrates the importance of expressing the placenta early when using this technique. It is interesting to note that there was no bleeding in spite of the retention of the placenta.

When comparing my estimations with other published figures, the results are found to be similar.

Davis and Boynton,<sup>13</sup> using this method in a series of 1020 cases, found that in 81 per cent. of them the blood loss was less than 100 c.c., while in only  $\frac{1}{2}$  per cent. was it greater than 500 c.c. In 73 per cent. of these cases the third stage lasted less than three minutes and manual removal was required in 1 in 127 cases. They compared this method with using Ergometrine either intravenously or intramuscularly following delivery of the placenta, and discovered a very marked decrease in blood loss and shortening of the third stage.

Tritsch and Schneider<sup>14</sup> of New York, Bickers<sup>15</sup> of Richmond, and O'Connor<sup>16</sup> of Boston are of the same opinion.

Leff<sup>17</sup> of New York has criticised the use of Ergometrine, because he considers that whilst it definitely causes contraction of the uterus, it fails to achieve retraction and that when the effect of the drug wears off it often results in a severe delayed post-partum hæmorrhage. He therefore gives posterior pituitary extract. Greenhill,<sup>18</sup> in the 1945 *Year Book*, has denied this, and my own opinion has been the same, as I have not found it necessary to give further oxytocic drugs for delayed bleeding. If prolonged action with ergot is required, Chassar

Moir<sup>19</sup> has shown that liquid extract of ergot by mouth is most efficacious.

*Comments.*—In conclusion, therefore, I consider that the use of Ergometrine intravenously following the birth of the anterior shoulder provides no new mechanism, but that it hastens the normal process. It is important that it is given when the foetus is still distending the birth canal, otherwise it fails to get its maximum effect. Accurate timing is therefore of great importance. The effect on the uterus would appear to be sufficiently prolonged to prevent any delayed post-partum hæmorrhage. This method undoubtedly causes marked reduction in blood loss, which is a very important consideration in the pregnant woman, who is frequently anæmic in varying degrees, and at the same time it shortens the third stage (in itself not so important a factor except that once the placenta is away it is much easier to deal immediately with any episiotomy or tear that may have occurred). The disadvantages are that it requires an extra assistant to give the ergometrine at the optimum moment, and is therefore probably only suitable for institutional practice, where more help is available. A further possible danger is of giving it in a case of undiagnosed twins.

Occasional incarceration of the placenta may occur, but even so, blood loss appears to be less. Manual removal followed by prophylactic Sulpha and Penicillin therapy is rarely dangerous from the point of view of infection, provided that there has not been a massive hæmorrhage in the first place.

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## DISCUSSION

*Dr Fahmy* congratulated *Dr Callam* on the presentation of his paper which was the first on the subject of the management of the third stage of labour since *Dr Fahmy* discussed the subject at the Society's meeting many years ago. Some of those present would remember the late Professor Barger dealing with the value of ergot in midwifery, and his assertion that the British Liquid Extract contained no active component, yet subsequently the work of Chassar Moir had shown this view to be completely incorrect.

The management of the third stage of labour had offered fields for controversy. It was to be remembered that *Crédé* originally proposed his method in order to get rid of the placenta as soon as possible after the birth of the child; but it was open to argument whether *Crédé's* method had not, on the whole, done far more harm than good. *Dr Callam* had been giving ergometrine intravenously as a routine as the baby was about to be born in order to shorten the third stage and prevent hæmorrhage. *Dr Fahmy* had frequently used it intramuscularly just prior to the birth of the child's head, and he had only on two occasions to remove the placenta manually. It was possible that the rapid separation of the placenta might result in membranes being left behind in the uterus; but the speaker felt that after a long labour, especially one associated with inertia, intramuscular ergometrine had a useful place in preventing third stage hæmorrhage. The treatment of hæmorrhage in the third stage was primarily to stop the hæmorrhage, and ergometrine given intramuscularly or intravenously would be effective in the great majority of cases. Imprisonment of the placenta might occasionally occur; but as the bleeding was controlled, the patient's condition did not deteriorate, and removal of the placenta later could be undertaken, if necessary, with comparative safety. *Dr Fahmy* believed that midwifery nurses should be permitted to give ergometrine intramuscularly if bleeding in the third stage began—this would surely prove a wise procedure, and would generally prevent the necessity for a nurse to undertake more drastic measures under unfavourable circumstances.

*Dr Alexander* said he was very interested in *Dr Callam's* paper. It recalled to his mind the discussions which arose in 1922-23 in the old "Simpson" when induction by castor oil, quinine, and pituitrin was first tried out in Edinburgh. One case, a multipara, who went into labour following this method, ruptured her uterus. The late *Dr William Fordyce* carried out a very dramatic hysterectomy in the "lower labour ward," the patient making a good recovery, and the specimen was shown to the Society shortly afterwards. *Dr Alexander* was glad to hear *Dr Callam* had had no disaster of this kind with the use of ergot.

*Professor Kellar* also spoke.

*Dr Donald Shepherd* enquired whether there was any information regarding the liability of the ergot preparation to cause gangrene of the extremities.

*Dr MacGregor* said he would like to congratulate *Dr Callam* on his interesting paper. He thought that if his method of giving intravenous ergometrine when the anterior shoulder had been born proved satisfactory, it would be a godsend to the general practitioner, because if he could get over the third stage very quickly and could leave the patient with assurance that there would be no further bleeding, it would be a tremendous relief to him.

*The President* thanked *Dr Callam* very much for his most interesting paper. Papers on clinical research were interesting and illuminating and

would seem to be just as valuable as those gleaned from laboratory research ; there was great scope in a maternity hospital such as the Simpson to do such work, and he hoped that now the war was over there would be a steady flow of such papers.

The President said he also had been reminded of Professor Barger's paper on ergot. He remembered that paper well, and how at the old Simpson liquid extract of ergot was not used for five years or more because Barger had stated emphatically that it had no active properties, being prepared with water, whereas the American preparation was produced with alcohol and was active. He would like to think that this paper had been given when Chassar Moir was resident at the Simpson and had stimulated him to work on the subject and produce the great discovery he made some years later. It was very interesting that these two men had been in Edinburgh at the same time though one of course was much the senior.

The President thought that anything that could be found that would induce labour should be tried out thoroughly, because if they could get some certain drug or method, then the treatment of a number of cases, especially the toxæmias, would be greatly aided. The induction of labour with pituitary was brought here by Professor B. P. Watson from Canada. In the whole period which had elapsed since then, there had been only one case of uterine rupture following induction in the records of the Simpson Hospital, although drug induction of labour was very commonly used.

Dr Fahmy had mentioned the question of nurses being allowed to give ergometrine in very unusual circumstances. The C.M.B. was engaged in drafting new rules, and that point was one that was being considered.

Regarding Professor Kellar's point as to what should be taught to students at present, the President said that for the last two years he had been telling them that ergometrine might be given for this purpose, but that the practice was still *sub judice* at any rate in this country.

The hundred cases that Dr Callam had treated constituted a small number, but there had been a very large number in the United States and Canada so treated. Professor Edwin Robertson had been carrying out such treatment for the last six or seven years, and as he was still continuing to do so it was presumed that he had not had any bad results. The President said he would like, in conclusion, to thank Dr Callam very much on behalf of the Society for this, his maiden paper, and hoped that it would be the precursor of many.

*Dr Callam* replied to the discussion.

## BLOOD CHANGES IN THE AGED

By OSCAR OLBRICH, M.D., Ph.D., F.R.C.P.E.

*From the Biochemical Laboratory, Royal Infirmary, Edinburgh, and  
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THE increase in the average age of the population, and the diminution in the birth rate, make it essential that the "useful" life of every individual be as long as possible, and that the degenerative processes we associate with old age be prevented from appearing too early. The problem of ageing is, therefore, not only of academic interest but also a matter of great and increasing social and economic importance. It is obvious that we need much more information than is now in our possession on the essential changes involved in the process of ageing, and we need to distinguish these clearly from other, pathological, changes which occur more frequently in the aged but are not an actual part of senescence.

Ageing is a physiological process in which involution is the pre-dominant feature, and this involution begins in different organs at different times of life, at a rate conditioned by both internal and external factors. Although senescence is not in itself a disease, it leads to an increased susceptibility to disease. It is, therefore, of the greatest importance, in any investigation of ageing, to differentiate between the physiological process itself and the adventitious pathological changes which so frequently accompany it. Tissue dehydration, loss of elasticity of the connective tissue, cellular atrophy, increased cell pigmentation and fatty infiltration are generally considered to be structural changes inherent in the ageing person; whilst functional changes include progressive impairment of vision, hearing, memory and mental capacity. Chemical activity is also decreased generally, for not only is tissue repair slower in the aged, but the basal metabolic rate per unit of protoplasmic mass falls steadily with advancing years. These changes, which we regard as constituting part of the physiological process of senescence, produce conditions which in earlier life would be rightly interpreted as pathological. (We may instance emphysema, which, in the aged, is caused by the capillary bed reduction, resulting from the natural process of cell degeneration and atrophy.)

Changes in the composition of the blood might well be expected to accompany the many progressive degenerative processes in old age. Indeed such changes have frequently been reported, but a search of the literature reveals that different investigators have obtained results which are remarkably discrepant and indeed contradictory. Some of the reported figures are so far removed from the "normal" as to raise the suspicion that they refer, not to the physiologically

aged, but to patients suffering, in old age, from a variety of pathological conditions.

It seemed worth while, in these circumstances, to re-investigate certain aspects of blood morphology in relation to old age, since the peculiarly favourable opportunity was presented of examining a considerable number of old people living at Queensberry House, Edinburgh, under standard conditions in regard to nutrition, etc. Even in this group, of course, there was the difficulty, to which reference has been made, of deciding which individuals could be regarded as "normal." It is indeed rare to find an aged person without some "pathological" changes in the cardio-vascular or respiratory system. The rule adopted, on the basis of the argument outlined above, has been to regard as "normal," or rather as "physiologically aged," those who showed no distinct functional disturbance of a definitely pathological nature and in whom no gross organic lesions could be found.

#### METHODS

Blood for examination was invariably obtained in the early morning with the subject fasting and still in bed. It was withdrawn from the cubital vein without stasis, and avoiding cooling of the exposed arm. Part of the sample was added to the correct oxalate mixture in a Wintrobe tube and was used immediately for the morphological investigations. The remainder was prevented from clotting by addition of sodium oxalate and was used for determination of the plasma proteins and N.P.N.

Hæmoglobin was determined by the Haldane-Gower method using the standardised carboxy-hæmoglobin solution, with pipettes, and tubes calibrated by the National Physical Laboratory.

Red and white cells were counted by the standard procedure using a Neubauer counting chamber. For the differential count the Leishman staining method was used.

Blood sedimentation rate was determined by the Westergreen method, with readings at one and two hours.

Cell volume was measured by Wintrobe-tube method, centrifuging at 3000 r.p.m. for thirty minutes.

Plasma proteins and N.P.N. were determined by the micro-Kjeldahl method with duplicate analyses. Fibrinogen was obtained by recalcification of the plasma and separation of the fibrin; globulins were precipitated by saturation with magnesium sulphate at 20° C.

Erythrocyte diameters were determined by measurement, with calipers, of the magnified images projected on a ground-glass screen. The magnification was exactly 1000 (confirmed by measurement of a projected micro-scale) and 200 cells were counted in each stained, dried film.

The results from these various determinations were treated by standard statistical methods and compared with the results of similar investigations and with the most recent figures for young adults.

## RESULTS

*Erythrocytes*

The results of the red-cell counts are shown in Table I. For men over 60 years of age the mean is 5,075,000 and for women 4,761,000.

TABLE I  
*Red Blood Corpuscles*

Ages.	No. of Observations.	Mean Value $\pm$ Standard Error (in millions).	Range (in millions).	Standard Deviation (in thousands).
Males				
61-69 . . . .	10	4.943 $\pm$ .166	3.980-5.770	525
70-79 . . . .	23	5.126 $\pm$ .027	4.250-6.690	128
80-88 . . . .	8	5.097 $\pm$ .137	4.510-5.800	388
Females				
64-69 . . . .	9	4.863 $\pm$ .133	4.490-5.690	398
70-79 . . . .	20	4.798 $\pm$ .094	4.010-5.610	419
80-98 . . . .	19	4.680 $\pm$ .100	3.650-5.590	435
All Males . . . .	41	5.075 $\pm$ .081	3.980-6.190	516
All Females . . . .	48	4.761 $\pm$ .060	3.650-5.690	418
Males and Females				
61-69 . . . .	19	4.905 $\pm$ .104	3.980-5.770	455
70-79 . . . .	43	4.971 $\pm$ .079	4.010-6.690	519
80-98 . . . .	27	4.803 $\pm$ .088	3.656-5.800	457
All . . . .	89	4.906 $\pm$ .052	3.650-6.690	488

This table shows that there is practically no change in the red cell count with advancing years and also that there is no great difference between the sexes. It is significant that the sex difference after the climacterium decreases, the difference being only 250,000 per c.mm. at ages over 60.

Between the ages of 60 and 88 the men show no tendency to a fall in the number of red cells, and indeed those over 70 have a rather higher mean than those below, though this is of no statistical significance. The women, on the other hand, show a slight fall with increasing age, the mean values for the red-cell count being 4.86 millions for the 64-69 age group, 4.80 millions for the 70-79 age group, and 4.68 millions for those over 80. The differences are small, but the fact that they are both in the same direction supports the idea that they are real.

Comparison of these figures with those for younger people is not easy, since we are, unfortunately, dependent on the literature, having no younger "controls" of our own. The published figures cover an extraordinarily wide range, probably because of differences in the standard of "normal" and because of differences in technique, of which the taking of the blood sample is likely to be the most important. The careful work of Osgood (1935), who examined 259 males and 152 females, all young or middle-aged adults, gave a mean of 5.4 million red cells per c.mm. for the males and 4.8 millions for the females—figures almost identical with those of Wintrobe, who stated further

that there were no variations attributable to age (up to later middle life) or to geographical or racial distribution. In a very small series of aged people in Denmark, Rud (1922) found 5.14 millions for males and 4.77 millions for females, whilst Bing (1922), also in Denmark, but with some twenty in each group, found 6.1 millions for men and 5.1 millions for women. More recently, in the U.S.A., J. Millar (1939) gave an average of 4.46 millions for 150 aged persons, whereas Fowler *et al.* in 1941 found an average red cell count of 4.6 millions for males and 4.46 millions for females in 100 cases investigated. Newman and Gitlov (1943) gave an average of 4.42 millions for 50 men and 4.10 millions for 50 women. R. Isaacs (1943) found an average of 4.6 millions for males over the age of 50 (range 4.0-6.1) and for women 4.45 millions (range 3.9-5.5).

If we accept the results of Osgood and Wintrobe it appears that in old age men show a decided fall in the number of red cells (for the difference between our mean value in aged men and the mean value given by Osgood and Wintrobe in younger men is statistically significant) but that no such fall accompanying old age is evident in women. Such a procedure, however, is obviously unsafe. It may well be that recent wartime conditions have caused the normal red-cell concentrations to be lower than when the measurements of Osgood and of Wintrobe were made, and that, in actual fact, men show no diminution in red cells in old age, whilst women have an actual increase. Such an increase in the case of women might, indeed, be expected since at 60 the strain on the iron-metabolism due to menstruation and child-bearing has been removed. Evidence from hæmoglobin determinations, as will be seen later, supports this expectation, as does the tendency to a partial closing of the gap between the red cell counts of the male and female. It is noteworthy that Osgood found a mean difference of 600,000 between the red cell counts of his (young) men and women, whilst the mean difference in our series between the sexes, at ages above 60, was only 310,000, and at ages 60-80 only 250,000. This agrees with the findings of Newman and Gitlov (1943) whose difference was 310,000.

Nevertheless, a gap still remains between the sexes, and is statistically significant. This has an important bearing on the statement sometimes made that there is no real sex difference in red cell count or hæmoglobin and that the differences found so consistently in young adults are due to the extra strain on the blood-forming mechanism of the female and can be abolished by suitable dietary measures.

### *Hæmoglobin*

The findings of the Medical Research Council's Committee on Hæmoglobin Surveys afford a solid basis for comparison of the figures we have obtained, since we have used the methods recommended by the Committee and the interval between the two surveys was not likely to have been accompanied by any marked changes.

The Committee's report gives a mean figure of 102.2 per cent. for the hæmoglobin of 4560 men below the age of 60, and 93.7 per cent. for 7787 women of similar age. Among the men there was no difference between the married and single, but the hæmoglobin was slightly lower in the 50-59 group (mean, 101.5 per cent., 631 subjects) than in the 40-49 group (mean, 102.1 per cent., 1206 subjects) or the younger groups generally (mean, 102.7 per cent., 3223 subjects). For the men over 60 years of age it was still lower (mean, 98.7 per cent., 214 subjects). These differences are greater than are likely to occur by chance, but may be due to factors other than age—*e.g.* different occupations and dietary habits of the different age groups.

TABLE II

*Hæmoglobin*

Sex.	No. of Observations.	Mean Value.		Standard Deviation.		Range.		Standard Error of Hb per cent.
		Hb		of per cent.	of gm.	per cent.	gm.	
		in per cent.	in gm.					
Male . .	41	100.7	13.9	9.05	1.26	80-126	11.0-17.4	1.4 *
Female . .	47	94.6	13.2	9.34	1.29	72-116	9.9-16.0	1.4 *
All . .	88	97.4	13.5	9.65	1.35	72-126	9.9-17.4	1.0
Female								
Single . .	13	91.2	...	10.11	...	72-110	...	2.8 †
Married . .	25	96.8	...	6.16	...	90-116	...	1.2 †

The 47 women included 13 single, 25 married, 9 with state not recorded.

\* Difference of mean values and standard error of the difference:  $6.1 \pm 2.0$ .

† Difference of mean values and standard error of the difference:  $5.6 \pm 3.3$ .

In the group of men we have investigated (Table II), the mean hæmoglobin at all ages over 60 was 100.7, slightly (though not to a statistically significant extent) greater than the corresponding figure in the Medical Research Council Committee's report, but lower than that given for younger men. A curious fact is, however, that the mean value for the hæmoglobin in the age group 61-69 was 97.8 per cent., in the age group 80-88, 98.2 per cent., whilst it was 102.8 per cent. for the intermediate 70-79 group. This last figure was obtained in spite of the exclusion of a single abnormally high result—126 per cent.—from the group of 23 cases. Also it was not due to an analytical error in a single batch of samples, for each batch taken included blood samples from all age groups. It appears to be real, but what the explanation may be we cannot tell.

An exactly similar increase in the age group 70-79 is found among the women. For the age groups 58-69 and over 80, the mean hæmoglobin values were 94.4 per cent. and 92.4 per cent. respectively, whilst the value for the age group 70-79 was 97.0 per cent. The M.R.C. Committee's figure for "over 60" was just significantly

higher at 96.0 per cent. than our mean value for women of 94.6 per cent. The M.R.C. Committee's Report shows that women over 50 years of age have a mean hæmoglobin higher than those of the 20-50 age group, the difference being rather greater in single than in married women. At the younger ages, the married women tend to have rather lower hæmoglobin values than the single, but at ages above 50 there is no difference between the two. Since there was evidence that these same phenomena occurred in all the more homogeneous occupational groups, they appear to be connected with menstruation and child-bearing.

The general means for men and women over 60 were 100.7 and 94.6 per cent. respectively, and the difference was statistically significant. It is evident that the sex difference found in younger people persists

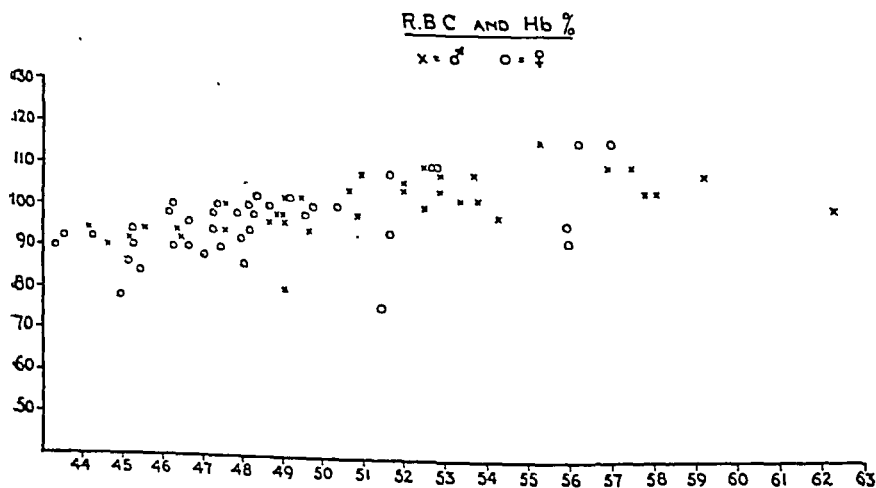


FIG. 1.—Scatter diagram showing correlation of Hb and erythrocytes in males and females.

in old age in spite of the fact that in men the hæmoglobin level tends to fall with advancing age, whereas in women after the cessation of menstruation it tends to rise.

The standard "100 per cent." used in the report of the M.R.C. Committee and in our own work corresponds to 13.8 gm. of hæmoglobin per 100 ml. of blood. Hence our mean values in aged persons were 13.9 gm. Hb/100 ml. for men and 13.2 gm. Hb/100 ml. for women, or 13.5 gm. Hb/100 ml. for both sexes. It may perhaps be worth while to compare these figures with others published in the literature, though the value of such comparison is minimised by the great variety of techniques employed. Williamson (1916) found 15.22 gm. Hb/100 ml. in persons up to the age of 75 and 15.67 gm. at higher ages; Cameron and Nicholson (1926) reported 15.66 gm. Hb/100 ml. for men over 60 years of age and 15.37 gm. for women; Millet and Balle-Hellaars (1932) stated that aged men and women had a mean hæmoglobin of 13.3 gm. Hb/100 ml., but other evidence in their paper suggests that their subjects were by no means normal; Nelson



and Stoker (1937) gave the figure 15.5 gm. Hb/100 ml. for aged American men and women; Millar (1939) in the same country found only 14.3 gm. Hb/100 ml.; Fowler *et al.* (1941) published 13.1 gm. Hb/100 ml. as the mean value for men over 60; Newman and Gitlov (1943) reported 12.7 gm. Hb/100 ml. as the mean value for men over 60 years old and 11.7 for women (*cf.* their similarly low values for the red cell count. It seems likely that their series included persons who could be regarded as definitely anæmic); Isaacs (1943) found 14.22 gm. Hb/100 ml. for men and 14.15 gm. Hb/100 ml. for women.

The correlation coefficient between erythrocytes and hæmoglobin was calculated, with its standard error— $1.02 \pm 0.047$ , showing clearly a positive correlation, which indicates adequate technique.

### Colour Index

It is fairly obvious from the data already presented that no great departure from the normal colour index is to be expected in the group of aged people we examined; indeed the mean value for the whole group was 0.98 with no statistically significant difference between the sexes or between the different age groups.

TABLE III

### Colour Index

Ages.	No. of Observations.	Mean Value $\pm$ Standard Error.	Range.	Standard Deviation.
Males and Females				
61-69 . . . .	19	$0.9832 \pm 0.014$	0.87-1.07	0.0595
70-79 . . . .	43	$0.9650 \pm 0.008$	0.75-1.06	0.0503
80-98 . . . .	27	$0.9948 \pm 0.014$	0.75-1.08	0.0732
All . . . . .	89	$0.9779 \pm 0.0069$	0.75-1.08	0.0643

### Hæmatocrit

Osgood (1935) found in the young a normal hæmatocrit reading in males of 45 c.c., with a range of 40-50, and for females 41 c.c., with a range of 36-45, whereas Wintrobe (1933) reports a normal hæmatocrit reading of 47 c.c. for males, with a range of 40-54, and of 42.4 for females, with a range of 37-47. Price-Jones, Vaughan and Goddard (1935) in 100 cases investigated found a mean volume of packed red cells of  $46.7 \pm 0.19$  per cent. with a range of 41.04-52.5 per cent.

In the aged, Newman and Gitlov give an average for the males of 41.2, with a range of 40.3-45.5, and for the females 36.7, with a range of 32-40. Isaacs (1938) states that aged males have a mean hæmatocrit reading of 45-46 per cent. and the females 41-42 per cent., whereas Fowler (1941) gives an average of 41.4-41.7 for males and 40.4 for females.

TABLE IV

*Hæmatocrit*

Sex.	No. of Observations.	Mean Value $\pm$ Standard Error.	Range.	Standard Deviation.
Male . . . . .	38	$45.14 \pm 0.54$	37-50	3.31
Female . . . . .	46	$42.02 \pm 0.78$	26-52	5.24
Male and Female . . . . .	84	$43.43 \pm 0.51$	26-52	4.71

In our investigation  $45.14 \pm 0.54$  is the average in the males for the three decades, with a range of 37-50. In the females, where 46 cases have been investigated, the average is  $42.02 \pm 0.78$ , with a range of 26-52.

In all findings one fact stands out, namely that the females show a lower hæmatocrit reading than the males.

Apparently there is an increase in males in the sixth and seventh decade which does not show up in the female group.

These findings, which also confirm those of recent British and American investigators, are significant because they provide evidence, which is contrary to many statements made, especially by older investigators, that in age neither hæmo-concentration nor hæmo-dilution takes place under normal conditions.

*Mean Corpuscular Volume*

Since, if we accept as a standard of comparison the carefully worked out figures of Osgood for young adults, our results for aged persons show little or no diminution either in total cell volume (hæmatocrit reading) or in the number of red cells per c.mm. blood, we must expect to find, in people over 60 years of age, a "normal" value for the mean corpuscular volume.

Starling (1920) found 72.2 c. $\mu$ . as the mean corpuscular volume in young adults, but all later workers have obtained higher values, probably as a result of improved technique, especially in the determination of total cell volume. Wintrobe and Millar (1929) arrived at a mean figure of 79.8 c. $\mu$ . Vaughan and Goddard (1935) reported an average for young and middle-aged men of 85.92 c. $\mu$ ., and Osgood (1935) for women of similar ages 88.5 c. $\mu$ . The usual text-book figure seems to be 88.2 c. $\mu$ . with a range of 76.5-98.1 (Wintrobe, 1942).

In our series of men and women over 60 years of age, the general average for the mean corpuscular volume was 88.9 c. $\mu$ .  $\pm 0.70$ , with a range of 60.6-100.4. For the men alone, the mean was 89.52 c. $\mu$ .  $\pm 0.69$ , and for the women alone 88.39 c. $\mu$ .  $\pm 1.15$ , so that there was significant sex difference. Both men and women showed a tendency for the mean corpuscular volume to increase with age. Although the differences between the age individually, smaller than necessary for statistical

fact that they were progressive suggests that they may have been real (Table V).

TABLE V  
*Mean Corpuscular Volume*

Sex.	No. of Observations.	Mean Value $\pm$ Standard Error.	Standard Deviation = $\sigma$ .	Range.
Male . . . .	38	$89.52 \pm 0.69$	4.25	79.4-97.5
Female . . . .	46	$88.39 \pm 1.15$	7.77	60.6-100.4
Male and Female . .	84	$88.90 \pm 0.70$	6.41	60.6-100.4

As in the case of other data, these results differ markedly from those for aged people published by Newman and Gitlov (1943). These workers found the mean corpuscular volume to be 97.7 c. $\mu$ . for men and 90.0 c. $\mu$ . for women. It is significant that they also obtained much lower red cell counts and hæmoglobin values than have been reported by the majority of other workers. It seems that their series of cases must have included subjects who were not really "normal" and might well have been classed as anæmic. Thus their group of women aged 65-69 had a mean hæmoglobin of 77.4 per cent. and a red cell count of 3.9 millions. In certain anæmias, including nutritional anæmia, the mean corpuscular volume is known to be high, and Mills (1925) has shown it to be subject to rapid fluctuation. It is perhaps worth noting that an increase in cell diameter of only 1  $\mu$  leads to an increase in corpuscular volume of approximately 44 per cent. and that, according to Mills, the corpuscular volume in anæmic patients may change as much as 18 per cent. within two hours.

Our figures for the mean corpuscular volume show a very slight increase when compared with those of Vaughan and Goddard (1935) and of Osgood (1935). This agrees with the slight decrease in the red cell count when our figures are compared with those of Osgood (1935) and the slight increase in our figures for the hæmatocrit reading compared with those of the same worker. It is permissible to suggest that this slight increase in the mean corpuscular volume in old age may be associated with the increased lactic acid content of the blood which has been reported (Loiseleur and Morel, 1931), and possibly also with the slight diminution in the plasma protein concentration, to which attention will be drawn in a later section of this paper.

#### *Red Cell Diameter*

Different values for the mean corpuscular diameter have been recorded by various investigators. These differences are probably due in part to the diverse methods employed, and in part to the technical difficulty of measuring the red cell diameter.

Apparently the most accurate method is the photographic one of

Ponder (1924), who measured the red cells in their natural environment, thus avoiding the most obvious error, namely that due to shrinkage in a medium inappropriate to the cell. Unfortunately, however, this method cannot be used for ordinary clinical purposes because of the difficult technical procedures involved.

Another accurate method is the diffraction method of Pijper, in which the mean cell diameter is calculated from a diffraction pattern formed by the cells placed in the path of a parallel beam of monochromatic light.

Most of the available figures are derived from measurement of the cell diameters in stained film, either by ocular micrometer or by projecting the image on a ground glass or photographic plate with known magnification, and measuring the diameter directly with calipers. In most investigations the projected image was traced and the tracing measured (Price-Jones). An eye-piece micrometer was used for direct measurement, and later this was improved by using a filar micrometer.

Among the factors known to affect the diameter of the red cells are dehydration (Saragea, 1927, showed that the red blood cell diameter increases during fasting), pH, and temperature. Price-Jones recorded diurnal variation, the maximum diameter being reached in the late afternoon and evening, and minimum diameter in the morning, the values being  $7.5\text{--}7.6\ \mu$  and  $6.9\text{--}7.1\ \mu$  respectively. These findings have been confirmed by Pijper with the diffraction method. Jørgensen and Warburg found the red cell diameter to vary in relation to meals and sleep. Violent exercise also influences the size of the red cell. Ponder and Millar have shown that the diameters measured in wet preparations are larger than in dried, or dried and stained films, the difference being about  $1\ \mu$ .

Of the many "normal" diameters recorded in the literature, a few may be mentioned in chronological order:—

1921.	Price-Jones	.	.	.	.	7.24
1924.	Ponder and Millar	.	.	.	.	8.8
1927.	Gram	.	.	.	.	7.8
1927.	Jørgensen and Warburg	.	.	.	.	7.7
1927.	Holler and Kudelka	.	.	.	.	7.6
1927.	McCormick	.	.	.	.	7.3
1929.	Price-Jones	.	.	.	.	7.202
1935.	Price-Jones, Vaughan and Goddard	.	.	.	.	7.17
1935.	Pijper	.	.	.	.	7.5

"Normal" values have been reported as low as  $6.5\text{--}6.0\ \mu$ .

Andersen and Mugrage (1936), Wintrobe (1930, 1934) and Osgood (1935) detected slight differences in red cell diameter in the sexes, the value for females being slightly greater ( $0.14\ \mu$ ) than for males, though in all cases the differences were so slight as to be statistically insignificant.

In the present investigation, samples of blood for examination were obtained from 23 men and 26 women all over 64 years of age,

and also from 10 healthy young persons (aged 20-30). Since no significant sex difference was found in the aged subjects, sex was not taken into account when comparing the results from the old and the young.

There are two ways of considering statistically the results of the measurements.

In the first method the mean diameter of the 200 cells measured for each individual is computed and taken as the mean corpuscular diameter for that individual; from the values so obtained for all individuals of a group, the mean corpuscular diameter of the group is calculated and, by the usual mathematical methods, the standard error, standard deviation and coefficient of variation are computed. These final figures measure the distribution and range within the group of the individual mean cell diameters.

The second method consists in taking the mean of all the cells measured for all the individuals in the group and calculating the standard error, standard deviation and coefficient of variation. This calculation gives the mean corpuscular diameter of the group as before, but the distribution is found for all the cells measured. Naturally the figures indicating the range or scatter are larger when the second method is used, but this method probably gives a truer picture.

TABLE VI  
*Red Cell Diameter*

	Average Age.	Average Size.	Standard Deviation $\sigma$ .	Standard Error.	Coefficient of Variation.
YOUNG 10 cases . . . . .	24.7	7.0 $\mu$	0.5418	$\pm 0.0542$	7.74%
OLD					
23 cases—Males . . . . .	74.2	7.6 $\mu$	0.7738	$\pm 0.0774$	10.18%
26 cases—Females . . . . .	77.9	7.6 $\mu$	0.8302	$\pm 0.0830$	10.92%
49 cases—Males and Females . . . . .	76.05	7.6 $\mu$	0.8080	$\pm 0.0808$	10.63%

Using the first method (calculation from individual means), for the group of 49 old people the following results are obtained:—

$$\text{M.C.D.} = 7.6 \mu \text{ (range } 7.1\text{--}8.0 \mu). \quad \text{S.E.} = \pm 0.027 \mu.$$

$$\text{S.D.} = 0.187 \mu. \quad \text{C.V.} = 2.46 \text{ per cent.}$$

Using the second method we obtain the following results:—

$$\text{M.C.D.} = 7.6 \mu, \text{ with a standard error of } \pm 0.081.$$

$$\text{S.D.} = 0.81. \quad \text{C.V.} = 10.63 \text{ per cent.}$$

Comparison of the aged males and females by the first method of calculation shows no significant difference at all. The second method, however, gives an indication that, although the mean corpuscular diameter for the two groups is the same, the range of variation is

slightly greater in the females than the males, the difference being so slight that it is not apparent when the individual means are used as the basis of calculation. The relevant figures are :

	Mean.	Standard Error.	Standard Deviation.	Coefficient of Variation.
Males . . . . .	7.6	$\pm 0.077$	0.774	10.18%
Females . . . . .	7.6	$\pm 0.083$	0.830	10.92%

It is thus fair to compare the aged and the young groups irrespective of sex.

The ten young people examined gave, by the method of calculating from the mean value for each individual :—

$$\begin{aligned} \text{M.C.D.} &= 7.03 \mu \text{ (range } 6.84\text{--}7.33 \mu). \quad \text{S.E.} = \pm 0.005. \\ \text{S.D.} &= 0.1611. \quad \text{C.V.} = 2.29. \end{aligned}$$

Calculation from the measurement of all cells gave, as in the older people, evidence of a much greater scatter, although the same value for the mean corpuscular diameter was obtained. By this method, the figures were :—

$$\begin{aligned} \text{M.C.D.} &= 7.0 \mu \text{ (range } 6.84\text{--}7.33 \mu). \quad \text{S.E.} = \pm 0.0542. \\ \text{S.D.} &= 0.5418. \quad \text{C.V.} = 7.74 \text{ per cent.} \end{aligned}$$

Whatever the method of computation, it is evident that the mean corpuscular diameter is significantly greater in the aged, and the detailed method shows further that the scatter, or range of variation, is also much greater in the aged.

Fowler *et al.* (1941) give the mean corpuscular diameter as  $7.5 \mu$  in the aged, a figure not significantly different from our own. Price-Jones (1922) found the mean corpuscular diameter to be  $7.69 \mu$  in aged persons, and stated that this was  $0.5 \mu$  greater than the average he found in normal (*i.e.* younger) individuals. He expressed the opinion that an increased diameter in the aged was associated with some degree of emphysema. Jørgensen and Warburg (1927) observed that "normal" individuals have less than 15 per cent. erythrocytes with a diameter equal to or greater than  $8.6 \mu$ . In the present investigation only 1.35 per cent. of the cells of young people had a diameter of  $8.5 \mu$  or more, whereas the corresponding figure for the old was 16.43 per cent. On the other hand, values of  $6.0 \mu$  or less were found in 9.55 per cent. of the young, but in only 4.87 per cent. of the aged subjects.

Price-Jones had a similar finding in his emphysematous patients. He explained the increased diameter of the red blood cell as due to an increased quantity of  $\text{CO}_2$  in the blood, carbonic acid tending to swell the red cells. The increased diameter in non-emphysematous aged persons might perhaps be explained by an increased lactic acid content of the blood, which has been stated to exist.

OSCAR OLBRICH

Whatever may be the explanation for the increased diameter in the red cell population in the aged, however, the fact is clearly demonstrated.

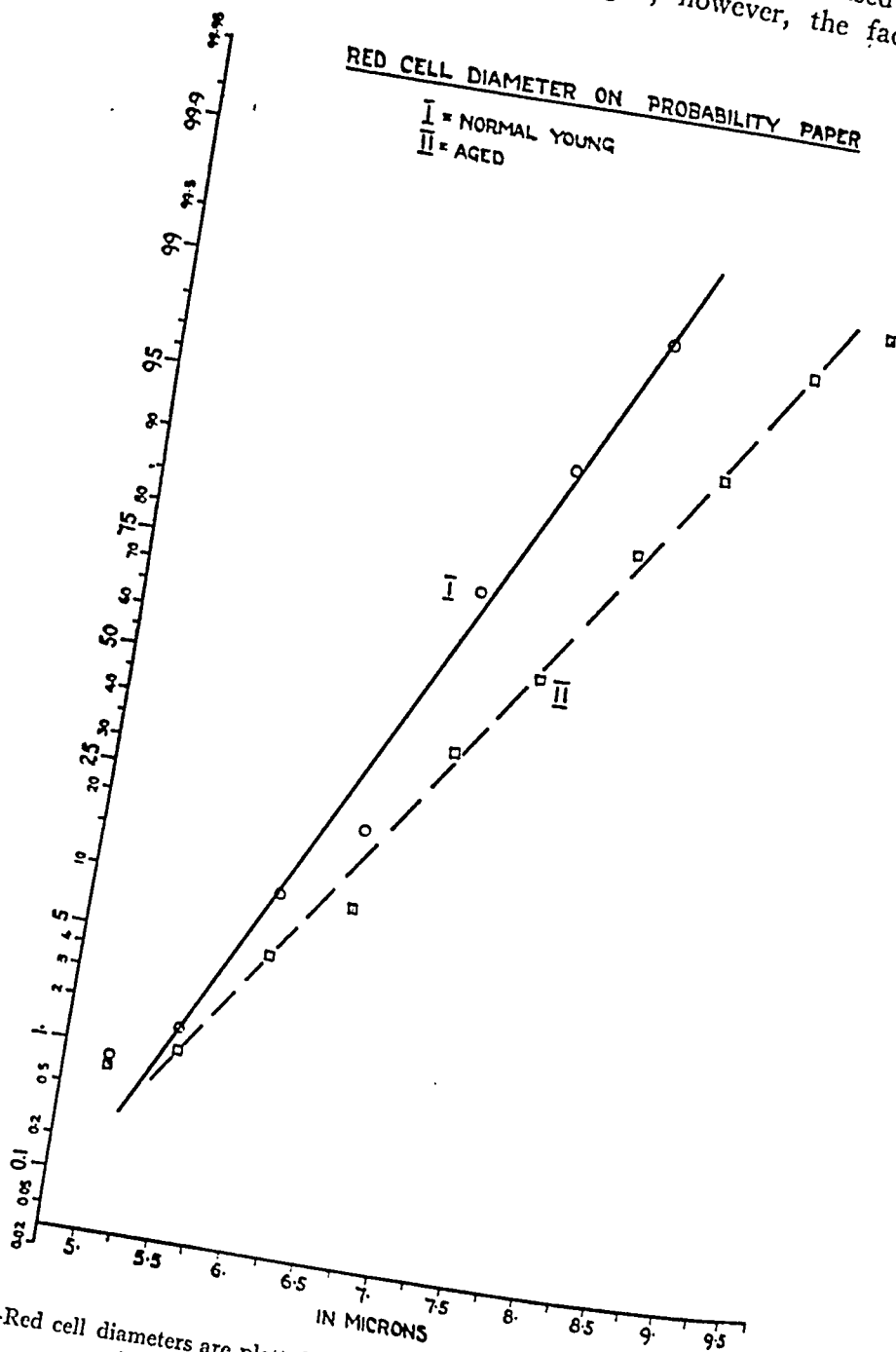


FIG. 2.—Red cell diameters are plotted on arithmetic probability paper. The difference in slope indicates the difference in standard deviation.

The greater variability in the cell diameters of the aged persons is also a matter of some significance. It may perhaps be explained by the supposition that in the aged the red cell population is maintained at a "normal" level with, however, a reduced rate of new cell formation

and a correspondingly reduced rate of cell destruction. This would mean that the blood of aged persons would contain relatively few young cells. Other differences between the blood of aged and young persons are also capable of being explained on this hypothesis, to which reference will be made again.

The eccentricity of the red cell was measured by taking the smaller diameter of the oval and the larger one. The formula  $\sqrt{1-b^2/a^2}$  gives the eccentricity and the value of 0.455 has been found, with no statistically significant difference between the aged and young subjects.

### *The White Blood Cells*

*The Total Count.*—The white cell count was performed on 89 aged subjects, 41 males and 48 females, under the experimental conditions already described. With the subjects grouped according to their age in decades, the average white cell count was calculated, with its standard error, standard deviation and coefficient of variation, for the two sexes separately. No age differences, however, could be

TABLE VII  
*White Blood Cells*

Sex.	No. of Observations.	Mean Value $\pm$ Standard Error.	Standard Deviation $= \sigma$ .	Range.	Coefficient of Variation.
Male . . .	41	7020 $\pm$ 200	1272	4600-9000	18.1%
Female . . .	48	7058 $\pm$ 243	1688	3200-12,800	23.9%
Male and Female .	89	7040 $\pm$ 160	1510	3200-12,800	21.4%

detected. The average mean value for the 41 males between 61 and 88 years of age was 7020  $\pm$  200 with a standard deviation of 1272 and coefficient of variation 18.1 per cent. For the 48 females between 61 and 88 years of age the average value was 7058  $\pm$  243 with a standard deviation of 1688 and coefficient of variation 23.9 per cent. Thus practically no difference in the white cell count could be detected in relation to sex or age; for both sexes together the average value was 7040  $\pm$  160, with a standard deviation of 1510 and coefficient of variation 21.4 per cent.

These figures, for healthy old persons, are within the range generally accepted as normal for younger persons, and do not confirm the findings of Newman and Gitlov (1935) that there is a difference between the two sexes in the aged, the males having a greater white cell count. J. Millar (1939) investigated 160 aged subjects and found the white cell count within normal limits. Fowler, Stevens and Stump (1941) investigated 100 old subjects, obtaining an average of 7220 white cells.

In the young, similar averages were found by Osgood (1935), investigating 269 subjects between 19 and 30 years of age. His average



was 7400. Price-Jones, Vaughan, Goddard (1935) gave an average white cell count of  $8007 \pm 221$ . Garley and Bryan (1935) gave an average white cell count of 7400 in subjects between 19 and 30 years of age, with a standard deviation of 1460 and coefficient of variation 24 per cent.

The range of variation of the published figures may be due in part to the fact that some workers have used capillary blood and others venous blood. It is, however, safe to conclude that in old age the total number of white cells is not significantly altered.

*The Differential Count.*—The polymorphs have been counted according to their lobes (Arneth-Schilling count), the subjects again

TABLE VIII

*Polymorphonuclear Count According to Lobes*

Sex.	No. of Observations.	Youth.	2 Lobed per cent.	3 Lobed per cent.	4 Lobed per cent.	5 Lobed per cent.
Male . . . . .	46	0.06	6.27	56.7	29.4	7.38
Female . . . . .	58	1.47	4.12	59.0	28.0	7.81
Male and Female . . .	104	0.01	4.8	55.1	32.8	7.25

being classified according to age and sex. There is a definite shift to the right, *i.e.* an increase in the percentage of the four and five-lobed cells. (This last group includes all the cells possessing 5 lobes or more.)

Arneth gives as normal for 3-lobed cells a value of 41 per cent., for 4 lobes 17 per cent., and for 5 lobes or more 2 per cent. There is a considerable increase in lobation of the polymorphs in the aged. For the whole group the mean value for 3-lobed cells was 40.3 per cent., for 4-lobed cells 24 per cent., and for cells with 5 or more lobes 5.3 per cent.

At the same time, it has been observed that the more lobes a polymorph possesses, the fewer are the granules contained in its cytoplasm. This increase in lobation bears a direct correlation to the decrease of the granules; in some cases 7- and 8-lobed polymorphs were observed with no granules at all. The generally accepted view is that the longer the white cells have remained in circulation, the greater the number of nuclear lobes, the decrease of the cytoplasmic activity being represented by the decrease in the number of granules and their final disappearance.

The actual length of time that a leucocyte is in the circulation is unknown. Roberts and Kracke (1930) made very thorough investigations in agranulocytosis and concluded that the leucocytes disappear in about 4 days from the circulation. A similar result was obtained by Weiskotten (1930) who paralysed the bone marrow with benzol in rabbits. Bunting (1938) denies that the lobation of the leucocytes

is an index of their age and states that lobes are not added one at a time and that a 5-lobed cell may be as young as a 3-lobed one.

TABLE IX

*Differential Count of White Blood Cells*

Mean Values.														
Sex.	No. of Observations.	Baso.	Eos.	Myelo.	Youth.	2.	3.	4.	5.	Lympho.	Mono.	Baso.	Eos.	Myelo.
Male . .	46	0.5	2.3	0	0.04	4.5	40.7	21.3	5.3	22.9	2.3	0.3	0.7	0
Female . .	58	0.6	1.9	0	0.1	2.8	40.1	19.6	5.3	27.0	1.8	0.4	0.8	0.1
All . .	104	0.5	2.1	0	0.07	3.5	40.3	24.0	5.3	25.1	2.0	0.4	0.8	0.1

Ranges.							
Sex.	Youth.	2.	3.	4.	5.	Lympho.	Mono.
Male . .	0.1	0.12	17.61	7.34	1.14	10.46	0.8
Female . .	0.1	0.11	19.56	7.34	1.16	12.45	0.8.6
All . .	0.1	0.12	17.61	7.34	1.16	10.46	0.8.6

There is, however, considerable evidence, also experimental, that polylobation is correlated with the ageing of the cell. Crossman and Chariper (1938) have shown in their experimental work that not only the time factor, but an increased activity of the cell is responsible for their lobation. All the investigators agree that the granules of the cytoplasm are an expression of protoplasmic activity; the decrease of these granules is a sign of decreased vitality.

If, then, one accepts increased lobulation and decreased granulation as indicative of increased cell age and decreased vitality, it appears that in ageing persons an increased number of white cells circulate in the blood, the vitality of which is decreased. These cells are older than the average white cell of younger persons, and although quantitatively there is no difference in the white cell population of the aged, there is a distinct qualitative difference.

The lymphocytes have the same average value as in the young and no difference could be detected in the cytological behaviour.

The basophil and eosinophil leucocytes have the same average values in the old as in the young. Their cytological behaviour with our methods of investigation did not display any morphological change. This is also true of monocytes.

# BRONCHIAL OCCLUSION IN CHILDHOOD TUBERCULOSIS: ITS PATHOGENESIS AND EFFECTS \*

By JAMES H. HUTCHISON, O.B.E., M.D., F.R.F.P.S.G., M.R.C.P.

INTRODUCTION.—Those of us who have had much to do with the diagnosis and treatment of primary tuberculous infection in childhood have always been intrigued by the cases in which there are massive X-ray shadows in the lungs without any marked degree of toxæmia or much in the way of respiratory distress. This condition was first outlined by Eliasberg and Neuland in 1920, *i.e.* soon after satisfactory films of the chest were technically possible, and to it they gave the name of epituberculosis. It has been widely accepted that the extensive shadow seen in the radiograph represents a non-specific pneumonic consolidation occurring around the Ghon's focus and that it is allergic in origin. At least this is a plausible theory. Such patients usually progress to recovery, however, and as far as I know such a condition has never been demonstrated histologically.

I would like to put forward the view with evidence in its favour that such X-ray shadows do not indicate pneumonic consolidation at all but are due to the presence of absorption collapse produced by bronchial occlusion. The occlusion of the bronchus is most often caused by the extrinsic pressure of enlarged tuberculous lymph glands on the bronchial wall sometimes in combination with sticky mucus produced by a swollen hyperæmic mucous membrane; in some cases a caseous tuberculous gland adheres to the bronchial wall and ulcerates into its lumen with the production of granulation tissue therein. All these changes have been observed through the bronchoscope and the existence of bronchial occlusion can be demonstrated by lipiodol bronchography. In this form of absorption collapse as in any other, bronchiectasis may develop although it differs from that due to pyogenic infection in being uninfected—at least for many months. Bronchial stenosis is also a rare sequel.

CLINICAL FEATURES.—A review of the clinical findings reveals that although the diagnosis of tuberculous infection can be confirmed in every case by the presence of positive tuberculin skin tests, the clinical signs are rarely such as to enable an accurate diagnosis of absorption collapse to be made. Dr Graham and I have recently analysed a series of 45 cases and in only 19 were local signs detected clinically such as impairment of percussion note, diminished air-entry, bronchial breath sounds, or scanty râles. In 5 cases only was there clinical evidence of mediastinal shift to the affected side. However,

\* Read to the Tuberculosis Society of Scotland at a meeting held at Mearnskirck Hospital, Renfrewshire, on 24th January 1947.

now that the true nature of these cases has been recognised, the finding of minor localising clinical signs in a child not acutely ill and with positive skin tests is regarded as indicating with little likelihood of error that further investigation will demonstrate the presence of pulmonary collapse. This clinical diagnosis is thus made by a process of deduction from past experience and from the knowledge of the pathological course often pursued by primary tuberculosis and is not based on the clinical signs alone, which do not by themselves justify any such clearly defined diagnosis. As experience and insight into this condition has been acquired we have come to regard another clinical sign seen in other 15 of our cases as being strong presumptive evidence in favour of bronchial occlusion. I refer to a history of asthma-like or wheezy breathing or of spasms of nocturnal cough with respiratory distress. In some cases an "asthmatoïd" wheeze is clearly audible with the stethoscope at the open mouth or there are rhonchi over the lung fields without the other accompaniments of asthma. The significance of this syndrome of wheezing or noisy breathing in a young child is so great as to make it advisable to exclude tuberculous infection in all such cases before affixing to them the label of "asthma."

As regards the *constitutional upset* it seems probable that the occurrence of collapse is associated with some fever and mild toxæmia in all or most cases. In a few there is an acute initial onset with brisk fever, abdominal pain, listlessness, anorexia, dry cough, and loss of weight. It must be stressed, however, that the occurrence of pulmonary collapse may be attended by such minimal upset that neither the child nor his parents are in any way concerned by it. Undoubtedly many children with a primary tuberculous infection complicated by pulmonary collapse pass through the complete illness unsuspected, and it is probably from this type of case that the bronchial stenosis or uninfected upper lobe bronchiectasis discovered by routine examination in adult life arises.

**RADIOLOGICAL FINDINGS.**—Radiographic appearances of *collapse* are not difficult to recognise as a rule, although they frequently are misinterpreted as being the appearances of consolidation. The right upper or middle lobes are most frequently affected, next in frequency come the left upper and lower lobes; the right lower lobe is rarely affected. Brock has explained this incidence on the anatomy of the tracheo-bronchial and broncho-pulmonary glands.

Radiological evidence of *mediastinal or tracheal shift* to the affected side was found in only 17 of our 45 cases. Other classical signs of collapse such as elevation of the diaphragm or "crowding" of the ribs were not seen in any case. I suggest that the comparative infrequency of these signs of collapse is to be attributed to the fact that when the bronchial lumen is occluded gradually (as in a slow process like tuberculous hilar adenitis), and especially if parenchymal tuberculosis is present in the affected lobe or sector, the outpouring of

fluid into the tissues may be more rapid than the absorption of air, so that the volume of the lobe may be as great as or actually greater than that of the normal lobe. Such a filled or "drowned" lobe is not atelectatic in the true sense of "imperfect expansion" although its aerating surface is as inadequate as an atelectatic lobe. The term *absorption collapse* better describes the state of affairs.

The presence of partial *bronchial occlusion* may also, on occasions, produce the opposite of absorption collapse. Thus partial obstruction by extrinsic pressure associated with a swollen hyperæmic mucous membrane may allow entry of air to the alveoli distal to the site of the bronchial narrowing during inspiration when the bronchi normally dilate slightly, but during expiration the slight narrowing of the bronchus may result in complete obstruction at the narrowed part of the lumen so that the exit of air cannot take place. This causes ballooning of the air-spaces or obstructive emphysema.

The suggestion that pulmonary collapse may be brought about by occlusion of bronchi by pressure of glands is far from new. In 1850 Gairdner cited a case so similar to those under discussion and described so completely that I think you will be interested to hear the main details. It is of a child of 5 years who died of "tubercular hydrocephalus." At autopsy the primary focus—recognised as such by Gairdner—was the size of a walnut and situated in the upper margin of the left lower lobe. The enlarged glands at the root of the lung pressed upon some of the bronchi going to the left lower lobe causing collapse of the anterior extremity of this lobe. In his article he says: "*I think the frequency of collapse of the pulmonary tissue both in the adult and in the child must now be considered as established and its connection with bronchial obstruction rendered at least extremely probable.*" Gairdner also quotes Carswell, writing some years earlier, who "figured the case of a monkey in which the left bronchus was much compressed or rather obliterated by a mass of tuberculous glands." The corresponding lung, he goes on to say, had diminished to less than a third of its normal bulk while the opposite lung, of which the bronchus was free, presented emphysema in several places.

It is an interesting reflection on medical habits and customs that this work was apparently completely forgotten for close on one hundred years because it is only within recent years that the importance of bronchial occlusion as a cause of bronchiectasis and as an explanation of the collapse in the primary tuberculous infection has been recognised.

*Conclusion.*—It seems reasonable to conclude, therefore, that although primary tuberculous infection does produce spontaneous manifestations of allergy such as erythema nodosum and phlyctenular conjunctivitis, epituberculosis is not one of these manifestations. Rather does its explanation rest purely on a well-founded and easily demonstrated mechanical basis.

## NEW BOOKS

*The Bacterial Cell in its Relation to Problems of Virulence, Immunity and Chemotherapy.* By RENÉ J. DUBOS. Pp. 460, with Plates and Figures. London: Oxford University Press. 1945. Price 28s. net.

This is one of the most important books on bacteriology that have appeared for some time. In it are correlated large numbers of observations in what might appear to be unrelated aspects of the life and behaviour of bacteria, particularly in their relationship to the human body. When it is said that there are over 1000 references in the bibliography the magnitude of the author's task will be realised. The author himself has published numerous papers, chiefly on antigenic structure, and enzyme production by bacteria.

The chapters include an analysis of published work on the cytology of bacteria, the mechanism of staining properties, the analysis of cellular structure by biochemical and biological methods, the variability of bacteria, the nature of virulence, immunisation against bacterial infection, and on bacteriostatic and bactericidal agents. There is an additional chapter by C. F. Robinow on the nuclear apparatus and cell structure of bacteria, mainly as shown by the Feulgen and HCl-Giemsa methods of staining. There are numerous photographs, many taken by the electron microscope.

The bringing together and reassembling in one volume of so much information, much of which must have been missed even by workers making every effort to keep abreast of bacteriological literature, is a notable achievement. But it is the revelation of how much is *not* known, and the lines of thought and research suggested, that give this book a particular value.

*New Aspects of John and William Hunter.* By JANE M. OPPENHEIMER. London: William Heinemann. 1946. Pp. 188. Price 25s.

As Dr Beekman remarks in his foreword to this study of the famous brothers, "much has been written concerning their lives and accomplishments, but the subject is by no means exhausted."

Miss Oppenheimer will earn the gratitude of Hunterian scholars for her two illuminating essays, the first dealing with Sir Everard Home and the destruction of the John Hunter manuscripts, the second with some aspects of William Hunter's activities which have been neglected by previous biographers.

The name of Sir Everard Home is of ill repute in medical history. Home was not only John Hunter's brother-in-law, and his colleague and assistant for twenty years; he was also his chief executor. In this capacity he retained possession of Hunter's manuscripts relating to his great collection. Although repeatedly requested to draw up a descriptive catalogue, he failed to do so, and in July 1823, twenty years after John Hunter's death, he burned the major portion of the papers, having already, it was alleged, appropriated their substance for his own communications.

Miss Oppenheimer discusses the justice of the accusation and carefully reviews all the available evidence. She sketches the career of Everard Home, "a great practical surgeon" in the opinion of Sir Benjamin Brodie; "an excellent surgeon, but rough in his manners," according to another eminent surgeon, Sir Astley Cooper. Home became a Fellow of the Royal Society at the early age of twenty-nine, but his originality was suppressed, perhaps naturally, by that of his dynamic master. Nevertheless he was the author of so great a number of scientific papers that the titles alone occupy fifteen pages in an Appendix to the Author's essay.

William Clift, who figures as Home's chief accuser, had acted as John Hunter's faithful amanuensis since joining the Hunter household as a lad of seventeen, fresh

from his home in Cornwall. His diary, which has been preserved, is full of recriminations against Home, whom he regarded as a common thief.

Sir Benjamin Brodie was more lenient, regarding the act as unjustifiable and foolish, but unwilling to admit that Home could have used the rough notes with much advantage to himself. In his own defence, Sir Everard Home stated that in burning the notes he was carrying out John Hunter's wishes. It cannot be denied that it was an error of judgment, in spite of Hunter's instructions, but in the author's view it was not a deliberate crime.

The true story will probably never be known. Meantime, Miss Oppenheimer produces all the evidence with impartiality, and leaves the reader to form his own judgment of the ill-famed Sir Everard.

There is also much new material in the account of William Hunter and his contemporaries, which forms the second part of the book. Although primarily an anatomist, and rather obsessed by the greater brilliance of his younger brother, William Hunter, along with his compatriot William Smellie, raised obstetrics to the status of a science. His association with the Court, with David Hume the philosopher, and with the political life of his time, are matters neglected by his previous biographers but carefully discussed in the present essay. "William Hunter emerges as a figure of prestige in his own times as well as in the pages of medical history." The book is beautifully printed, and the copious notes and bibliographies enhance its value.

*Peripheral Vascular Diseases.* By E. V. ALLEN, B.S., M.A., M.D., M.S., F.A.C.P., N. W. BARKER, B.A., M.D., M.S., F.A.C.P., E. A. HINES, Jr., M.D., B.S., M.A., M.S., F.A.C.P., and associates in the Mayo Clinic. Pp.xii+871, with 386 illustrations, 7 in colour. W. B. Saunders Company. 1946. Price 50s. net.

George Elgie Brown joined the Mayo Clinic after ten years in general practice, and he decided to specialise in peripheral vascular disease; because it appeared to him that there was least knowledge and most confusion about this group of diseases. Naturally, he became an American pioneer in the field, and this book was planned by him.

Unfortunately, he died before he could carry out this part of his task, but the work has been brought to fruition by his distinguished team of collaborators at the Mayo Clinic.

The result is a complete and authoritative account of the peripheral vascular diseases; clearly written and profusely illustrated. The subject matter is developed in a systematic way, and a description of the anatomy; of the diagnostic approach; and of special methods of investigation precedes a consideration of individual diseases. A wide range of illnesses are described, from varicose veins to temporal arteritis.

Medical treatments, with their special techniques, and surgical procedures are fully dealt with, and the book concludes with a medico-legal section. An interesting book from which much may be learnt.

*The Pathology of Traumatic Injury.* A General Review. By JAMES V. WILSON, M.D., M.R.C.P. Pp.xi+192, with 61 illustrations (several in colour). Edinburgh: E. & S. Livingstone Ltd. 1946. Price 20s. net.

This little monograph is a summary of the literature on the pathology of trauma considered in the light of the author's personal work and war experience. The work has been produced during the stress of war, and so it has not been possible to consult several very important papers.

The book is divided into two parts, the first dealing with more general conditions—shock, burns, blast injury, etc.—while the second part deals with injuries of the various systems.

Some of the subjects are rather briefly discussed, as for example tension pneumothorax—an important traumatic condition whose possibilities are far-reaching. Little

is said about the pleural effusion after hæmothorax—when it occurs and the changes that take place in the blood after the first few hours. Fractures are dismissed in seven pages under Injuries of Bones and part of this is devoted to Fatigue Fractures, which are said to be non-traumatic, and aseptic necrosis in such conditions as Perthes and Keinboch's disease.

These are small matters, however, and what is there is good. The reading, however, leaves one with a feeling of something wanting—a book that with a more concise study of each subject might be something really good.

*Skin Diseases Nutrition and Metabolism.* By ERICH URBACH, M.D., F.A.C.A.  
Pp. xxii+634, with 266 illustrations. London: William Heinemann. 1946.  
Price 50s. net.

This book is described among other things as the first comprehensive presentation of the inter-relationship between dermatology and internal medicine and the first complete dietotherapy of skin diseases. It is divided into five parts. Part 1 deals with the influence of nutrition on the physiology of the skin, Part 2 with the nutritional causes of dermatoses. In Part 3 is discussed the influence of diseases of the gastrointestinal tract, liver and pancreas on the skin, and in Part 4 the nutritional therapy of skin diseases. Nutritional tables are found in Part 5.

Urbach stresses the importance of constipation in the production of disease, a view contrary to a modern tendency which belittles the effects of constipation. Few dermatologists, however, will agree with his views on papular urticaria. The author uses the word "porridge" in a sense new to Scottish readers at all events; here it does not contain flour. In the same way "corn" would here be called maize. There is lack of uniformity in the spelling of some of the words, while others are wrongly spelled; these, however, are minor blemishes.

The author has presented the subject in a fascinating manner, but at times with a wealth of detail that tends to be somewhat bewildering. Physicians as well as dermatologists would find much of interest and instruction. An extensive bibliography of 1400 references is given. The book could be read with advantage not merely by dermatologists but by all interested in nutrition and dietetics.

*The Human Approach.* By HENRY YELLOWLEES, O.B.E., M.D., F.R.C.P., D.P.M.  
Pp. 189. London: J. & A. Churchill Ltd. 1946. Price 10s. 6d. net.

It has been said that every medical student should be compelled to attend a class in logic, the reason of course being that his attention is so apt to become focussed on methods of precision and the scientific aspects of his studies, to the exclusion of that which is common sense and personal. This delightful book is a corrective which might be prescribed as a holiday task at the commencement of the clinical years, the reader being asked later to give an appreciation in the form of an essay.

Very skilfully, in his preface, the author anticipates criticism of style and form, but in reality there is no need, since the motive is soon apparent and often points are pushed home by the very unusualness of expression at which Dr Yellowlees is a past master. Much humour is found in his pages which reveals a sharpened wit and sympathy with the foibles of mankind that can only come from a wide and deeply interested experience.

Each of the fifteen chapters treats a different aspect; all are extremely good, but those on "case taking" and "doctor and lawyer" are perhaps outstanding. However, each reader is bound to find somewhere in this wealth of practical material some cord which creates a special bond of understanding. It is such a pleasure to find a fearless author who can strike a new note and point the way to an understanding of what a medico's real rôle should be.



*Edinburgh Post-Graduate Lectures in Medicine.* Vol. Three. Pp. 586. Edinburgh: Oliver and Boyd. 1946. Price 15s. net.

Within the last year Post-Graduate teaching has become a major activity of the Edinburgh Medical School, with its intensive courses in both medicine and surgery. During the war, however, it was almost entirely confined to the Edinburgh Post-Graduate Lectures sponsored by the Honyman Gillespie Trust, which continued at regular intervals. Thirty-two of these lectures, delivered during 1942 and 1943, are now published in this third volume of the series. The lectures do not appear in the order in which they were given, but are grouped, as far as is possible, according to their subject, and their interest is enhanced by this arrangement. None of the lectures is concerned with the medicine or surgery of warfare and few with war-time conditions, so that the volume has lost nothing by delay in its publication. The activities of the Edinburgh School are widely represented and a great deal of most useful and interesting information is provided. These volumes are published under a grant from the Honyman Gillespie Trust.

*Principles in Roentgen Study of the Chest.* By WILLIAM SNOW, M.D. Pp. 414, with 508 illustrations. Springfield, Illinois: Charles C. THOMAS. 1946. Price \$10.

The author starts by describing the radiological appearances of the average lung and points out that these vary with age. The remaining chapters explain and describe the changes found in all phases of pulmonary disease, and also the appearances associated with cardio-vascular lesions. The illustrations are extremely clear and well chosen reproductions of X-ray plates. In many cases there are serial pictures to show the progress of the disease process and the response to treatment, and the history and clinical findings are briefly given. This book has been written for the clinician, and both the text and the illustrations should prove extremely helpful in diagnostic problems, showing how best radiological examination can assist in the diagnosis and management of different pathological processes. The book can be cordially recommended to all physicians who are interested in chest disease.

*Jonathan Hutchinson: Life and Letters.* By HERBERT HUTCHINSON. Pp. viii+257, with 12 plates. London: William Heinemann. 1946. Price 12s. 6d.

This biography of Jonathan Hutchinson is welcome as a portrait of the man rather than as a record of his professional achievements. The author is not himself a medical man, but he has had access to much authoritative information from family records and personal letters.

As a background we have a sketch of the austere life of a rigid Quaker family in Yorkshire, the influence of which on the evolution of Hutchinson's intellectual and emotional life is clearly traceable. This is borne out from the many letters, mostly addressed to his wife, which are here reproduced.

His very versatility makes it difficult to assign to Jonathan Hutchinson his proper place among the distinguished men of his own time, of which he certainly was one. Traditionally he is remembered as a surgeon, but he was much more than that. Sir William Osler said of him. "He is the only generalised specialist which the profession has produced, and his works are a storehouse upon which the surgeon, the physician, the neurologist, the dermatologist and other specialists freely draw, . . . he is a man with a truly Hunterian mind . . . and bears a strong likeness to the immortal Hunter."

A generation which is in danger of forgetting what clinical knowledge owes to Jonathan Hutchinson would do well to read this book.

## NEW EDITIONS

*Electrocardiography.* By LOUIS M. KATZ. Second Edition. 1946. London: Henry Kimpton. Pp. 883, with 524 figures. Price 6os. net.

The results of the first twenty years' work with Einthoven's new instrument were embodied in the classical monographs of Lewis (1925) and Wenckebach and Winterberg (1927), which for many years were the standard works of reference on the subject. In the last twenty years a marked re-orientation of research has occurred, and attention has been directed more and more to the condition of the ventricular muscle and in particular to the effects of coronary disease. Of recent years a number of text books dealing with this highly specialised branch of medicine have appeared and one of the most important is the book under review. In this exhaustive work the change in outlook is reflected in that the arrhythmias constitute less than half the text, while the sections on coronary disease, hypertrophy and other myocardial affections predominate.

The basic principles of the subject are adequately dealt with and the standards of normal in the various deflections in the electrocardiogram are fully discussed. Full use is made of præcordial leads and their usefulness illustrated and discussed. A noteworthy addition to the section on arrhythmias is the description of Interference-Dissociation, so long neglected in English as opposed to Continental text books.

The illustrations are of high technical quality, well reproduced, well chosen and abundant. The book, however, is far more than a clinical atlas of electrocardiography. It sets out to explain the genesis of the curves and the mechanism of arrhythmias, and achieves considerable success.

The well-informed and experienced reader may not always agree with the theoretical arguments of Dr Katz. The interpretation of the genesis of coronary curves, for example, differs considerably from that of Wilson and others, and the conception of "heart strain patterns" savours of heresy to many. The book contains many expressions of personal opinion, and to the beginner is on that account somewhat dangerous reading if not balanced by acquaintance with other viewpoints. In common with many American publications to-day the bibliography refers principally to American literature even in fields in which British and Continental pioneer work was outstanding.

The book, though hardly a primer for the uninitiated, is recommended as well worth studying by those who already have some knowledge of the subject.

*The Diabetic A.B.C.* By R. D. LAWRENCE, M.A., M.D., F.R.C.P. Ninth Edition. Pp. vii+79. London: H. K. Lewis & Co. 1946. Price 4s. net.

This small book, written for patients and nurses, has long been the diabetic's guide. It is mostly concerned with diets, but also contains some helpful advice on the use of insulin and on what to do when ill. A short addition deals with the present post-war changes in food rationing.

*Microbiology for Nurses.* By MARY E. NORSE, M.D., and M. FROBISHER, S.B., SC.D. Seventh Edition. Pp. xii+521, with 214 illustrations. London: W. B. Saunders Co. Ltd. 1946. Price 15s. net.

This book deals with bacteria, viruses, protozoa, yeasts and moulds, and contains much information likely to be useful to the practising nurse. There are chapters on infection and resistance, hypersensitiveness, and on sepsis, disinfection and sanitation. This new edition has been revised in the light of recent advances and is well up-to-date. Its continued usefulness and popularity are assured.

*Forensic Medicine.* By DOUGLAS J. A. KERR, M.D., F.R.C.P.E., D.P.H. Fourth Edition. Pp. xii+359, with 89 illustrations and 4 plates. London: A. & C. Black Ltd. 1946. Price 18s. net.

We are glad to be able to welcome a further edition of this excellent work. Dr Kerr has managed to introduce some new matter, especially in the chapter on head injuries. The section on blood grouping has been completely rewritten and a number of new photographs have been included. The book should continue to appeal to the medical practitioner as well as to the undergraduate.

*Clinical Practice in Infectious Diseases.* By E. H. R. HARRIES, M.D. (LOND.), F.R.C.P., and M. MITMAN, M.D. (LOND.), F.R.C.P. Third Edition. Pp. 679, with 56 illustrations. Edinburgh: E. & S. Livingstone. Price 22s. 6d. net.

This useful and comprehensive volume has been brought up-to-date in its new edition. The general problems of immunity, diagnosis, and management and control of infectious diseases are considered and much useful information provided. The chapter on chemotherapy contains a survey of the uses of the sulphonamides, particularly the newer compounds, and of penicillin, and a short note on streptomycin is included. An account of the pneumonias is a recent addition and contains a review of modern opinion of primary atypical and the other virus pneumonias. Like its predecessor, the edition contains many references to the literature and the efforts of the authors to present a comprehensive picture of modern fever practice are highly successful. This book was originally intended for students of infectious diseases, but it contains a great deal that is of interest to the general physician.

*A Descriptive Atlas of Radiographs.* By A. P. BERTWISTLE, M.B., CH.B., F.R.C.S.ED. Sixth Edition. Pp. xxix+606, with 947 illustrations. London: Henry Kimpton. 1946. Price 45s. net.

In the latest edition of this *Atlas of Radiographs* the section which deals with the dental system has been considerably expanded, and a section devoted to helminthology has been started. There are, however, comparatively few changes. It would be an advantage if some of the older and less satisfactory reproductions could be replaced by more recent examples, and the author asks for the assistance of readers in this task.

The descriptive notes which accompany the plates might also well be revised. It is disconcerting to read that the markings seen in a normal chest film are formed by the bronchial tree and not by the pulmonary vessels. In a book primarily intended for clinicians and senior students this erroneous statement is bound to cause confusion.

*Textbook of Gynaecology.* By J. H. PEEL. Second Edition. Pp. xvi+467, with 218 illustrations. London: William Heinemann. 1946. Price 21s. net.

The appearance of a second edition of this book so soon after the first gives a measure of the latter's success. Although retaining the general design the author has made a thorough revision. The chapter on anatomy has been expanded and new material added to bring the sections dealing with the growing edges of the subject up-to-date, namely physiology, endocrine disorders and sterility. The inclusion of an appendix of the numerous proprietary hormone preparations will prove useful, but shows the great benefit that would accrue if the chemical firms would agree to a standardisation of nomenclature for similar preparations.

Clearly written, the book reads easily and the illustrations are good and well reproduced. This volume can again be confidently commended to the senior student as well as to the general practitioner who is looking for a concise, yet balanced and comprehensive statement of modern gynaecological teaching.

*Synopsis of Pathology.* By W. A. D. ANDERSON, M.A., M.D., F.A.C.P. Second Edition. Pp. 741, with 327 illustrations. London: Henry Kimpton. 1946. Price 32s. 6d. net.

This edition has been completely revised and greater emphasis has been given throughout to tropical diseases and conditions important in War Medicine. Subjects such as infective hepatitis and blast injuries are dealt with at length while many other changes and additions have been made. The book is a concise but comprehensive presentation of pathology and will be of value to both student and clinician, filling in the gap between modern pathology and clinical medicine.

*An Introduction to Bacteriological Chemistry.* By C. G. ANDERSON. Second Edition. Pp. x+500. Edinburgh: E. & S. Livingstone Ltd. 1946. Price 20s. net.

All bacteriologists will welcome the new edition of Dr Anderson's well-known text-book as an invaluable and much-needed tool. To the specialist, an essential work of reference, to the student a clear and readable text-book, it brings together a mass of information from widely-scattered sources. The reader is kept up-to-date even in such rapidly developing fields as chemotherapy, antibiotics, or growth factors; but the considerable expansion necessitated by new discovery is achieved without any obscuring of fundamentals, and the value of the book to the student wishing to acquaint himself with the essentials of the subject is not impaired.

The author treats his subject very ably from the point of view of the organic chemist, to whom this book will make a special appeal. The biochemistry of bacteria is fast exchanging the chemical for the physiological outlook, the static for the dynamic, as isolated chemical facts come into their true physiological focus. The value of this book would have been much enhanced had more of this new dynamic spirit been infused into it.

*Textbook of Bacteriology.* By R. W. FAIRBROTHER, M.D., D.SC., F.R.C.P. Fifth Edition. Pp. 8+480. London: William Heinemann Ltd. 1946. Price 17s. 6d.

Since first published in 1937 reprints or new editions of this book have appeared almost annually—a satisfying testimony to its usefulness and popularity.

In the present edition a thorough revision of the text has been made, out-of-date material has been removed, and the latest advances of recent years have been incorporated in a form suitable for the undergraduate.

## BOOKS RECEIVED

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| BENDA, CLEMENS E., M.D. Mongolism and Cretinism.<br>(Messrs William Heinemann (Medical Books) Ltd., London)   | 25s. net. |
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| BROWNE, O'DONEL T. D., M.B., M.A., M.A.O. (UNIV. DUB.), F.R.C.P. LOND.,<br>F.R.C.O.G. The Rotunda Hospital, 1745-1945.<br>(E. & S. Livingstone Ltd., Edinburgh) | 42s. net. |
| CAMERON, A. T., C.M.G., M.A., D.SC. EDIN., F.R.I.C., F.R.S.C. Recent Advances<br>in Endocrinology. Sixth Edition (J. & A. Churchill Ltd., London)               | 21s.      |
| CLARK-KENNEDY, A. E., M.D., F.R.C.P. Medicine. Vol. I. The Patient<br>and His Disease. (E. & S. Livingstone Ltd., Edinburgh)                                    | 20s. net. |
| CLAY, HENRY H., F.R.SAN.I., F.I.S.E. The Sanitary Inspector's Handbook.<br>Sixth Edition. (H. K. Lewis & Co. Ltd., London)                                      | 22s. net. |

- DEUTSCH, HELENE M. D. The Psychology of Women. Vol. II., Motherhood.  
(*Messrs William Heinemann Ltd., London*) 25s. net.
- GAARENSTROOM, J. H., and DE JONGH, S. E. Monographs on the Progress  
of Research in Holland. Contribution to the Knowledge of the Influence  
of Gonadotropic and Sex Hormones on the Gonads of Rats.  
(*Published by Elsevier, distributed by Cleaver Hume Press Ltd., London*) 16s. net.
- GRUNEBERG, HANS, PH.D., M.D. Animal Genetics and Medicine.  
(*Hamish Hamilton Ltd., London*) 21s. net.
- HARVEY, WILLIAM CLUNIE, M.D., D.P.H., M.R.SAN.I., and HILL, HARRY,  
F.R.SAN.I., F.S.I.A., A.M.I.S.E. Second Edition.  
(*H. K. Lewis & Co. Ltd., London*) 14s.
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(*H. K. Lewis & Co. Ltd., London*) 6s. net.
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Surgery. Third Edition.  
(*E. & S. Livingstone Ltd., Edinburgh*) 32s. 6d. net.
- KESTENBAUN, ALFRED, M.D. Clinical Methods of Neuro-ophthalmologic  
Examination.  
(*Messrs William Heinemann (Medical Books) Ltd., London*) 25s. net.
- KLEINER, ISRAEL S., PH.D., and DOTTI, LOUIS B., PH.D. Laboratory  
Instructions in Biochemistry. Second Edition.  
(*Henry Kimpton, London*) 12s. 6d. net.
- Standing Committee on Laboratory Methods, University of Glasgow. Notes  
on Clinical Laboratory Methods. Fifth Edition.  
(*John Smith & Son (Glasgow) Ltd., 26-30 Gibson Street, Glasgow, W. 2.*) 3s. 6d.
- LONDON, LOUIS S., M.D. WASHINGTON, D.C. Libido and Delusion. Second  
Edition (Enlarged) (*Mental Therapy Publications, Washington, D.C.*) \$3.50
- LOW, R. CRANSTON, M.D., F.R.C.P.E., F.R.S.E., and DODDS, T. C., F.I.M.I.T.,  
F.I.B.P., F.R.P.S. Atlas of Bacteriology.  
(*E. & S. Livingstone Ltd., Edinburgh*) 32s. 6d. net.
- McLACHLAN, A. E. W., M.B., CH.B. (EDIN.), D.P.H., F.R.S. (EDIN.). Handbook  
of Diagnosis and Treatment of Venereal Diseases. Third Edition.  
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- MICKS, R. H., M.D. (DUBLIN), F.R.C.P.I. The Essentials of Materia Medica,  
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(*J. & A. Churchill Ltd., London*) 18s.
- MINNITT, R. J., M.D., D.A. (R.C.P. AND S. ENG.). Gas and Air Analgesia.  
Third Edition . . . . . (*Ballière, Tindall & Cox, London*) 5s.
- PAINTER, CHARLES F., M.D. The 1946 Year Book of Industrial and Ortho-  
pedic Surgery . . . . . (*The Year Book Publishers, Chicago*) \$3.75
- RAPER, HOWARD RILEY. Man against Pain . . . . . (*Victor Gollancz Ltd.*) 10s. 6d.
- RUSSELL, C. SCOTT, M.A., F.R.C.S. EDIN., M.R.C.O.G. The Childbearing Years.  
(*Blackwell Scientific Publications, Oxford*) 7s. 6d. net
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(*H. K. Lewis & Co. Ltd., London*) 22s. 6d. net.
- SPILLANE, JOHN D., B.SC., M.D. (WALES), M.R.C.P. (LOND.). Nutritional  
Disorders of the Nervous System. (*E. & S. Livingstone Ltd., Edinburgh*) 20s. net.
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(*John Wright & Sons Ltd., Bristol*) 25s.
- Formerly by WALKER, NORMAN, KT., M.D., LL.D., F.R.C.P., and PERCIVAL,  
G. H. An Introduction to Dermatology. Eleventh Edition by G. H.  
PERCIVAL . . . . . (*E. & S. Livingstone Ltd., Edinburgh*) 35s. net.
- WEINEMANN, JOSEPH P., M.D., and SICHER, HARRY, M.D. Bone and Bones,  
Fundamentals of Bone Biology . . . . . (*Henry Kimpton, London*) 50s. net.
- WILLIAMSON, BRUCE, M.D. EDIN., F.R.C.P. LOND. A Handbook on Diseases  
of Children. Fifth Edition . . . . . (*E. & S. Livingstone Ltd., Edinburgh*) 3s. 6d.
- YOUNG, JAMES, D.S.O. A Text Book of Gynæcology. Seventh Edition.  
(*Adam & Charles Black, London*) 30s. net.
- ZOETHOUT, WILLIAM D., PH.D., and TUTTLE, W. W., PH.D. Textbook of  
Physiology. Ninth Edition . . . . . (*Henry Kimpton, London*) 25s. net.

# Edinburgh Medical Journal

July 1947

## THE PERFUSION EXPERIMENT IN THE STUDY OF TISSUE INJURY \*

By CHARLES H. KELLAWAY, M.C., M.D., M.S., F.R.C.P.(Lond.),  
F.R.A.C.P., F.R.S.

Director-in-Chief, The Wellcome Research Institution

WHEN tissue cells are subjected to the action of nocuous agents, all grades of injury may be produced, from the slightest to the most severe, and pharmacologically active substances and enzymes may be set free into the tissue spaces. For the study of such changes the perfusion experiment has some advantages. We can confine the injury to a single organ and readily grade its intensity and by using physiological saline as the perfusion fluid the estimation of active substances in the perfusate may be more easily effected than if the organ were perfused with whole blood.

On the other hand, such simplification has grave disadvantages. It alters the permeability of the walls of the vascular spaces in the perfused organ and must be responsible for some degree of injury to the tissues by destruction of normal osmotic balance, by the production of an abnormal hydrogen ion gradient from the cells through the tissue spaces to the vessels and by the maintenance of anoxia. It is indeed a matter for some surprise that these abnormal conditions should by themselves provide so little evidence of injury as indicated by the nature of the outflowing perfusate. But in evaluating the results we must constantly have in mind the injury caused by the perfusion, though it may not be of the gross kind which results from the action of the nocuous agents being studied.

The perfusion experiment cannot by itself provide proof that a pharmacologically active substance liberated from the tissue cells causes particular symptoms of injury in the intact animal. Other active substances not estimated in the perfusate may be liberated at the same time and may be responsible for, or may contribute to, the development of the symptoms. If, however, it can be shown that an active substance is set free by a nocuous agent and that its local action can account for certain symptoms there is a reasonable probability that it has this action in the intact animal.

\* Being the Seventh Sharpey Schafer Memorial Lecture delivered in Edinburgh on 22nd April 1947.

On the other hand, failure to demonstrate the liberation of a particular cell constituent in saline perfusion of an organ rich in it does not inevitably mean that such liberation plays no part in the production of symptoms. The nocent agent may depend for its activity on the liberation from the blood or from some other tissue of substances which cause the significant injury to the tissue cells, or may itself have injurious properties conferred upon it in the intact animal.

At the Hall Institute in Melbourne, Australia, during the course of several years, we used the perfusion experiment to study tissue injury by a variety of nocent agents. Our interest in this subject arose primarily from the work of Lewis and his colleagues<sup>1</sup> on the reaction of the blood vessels of the human skin to injury of the epithelium. Pricking, heavy stroking, freezing, burning, injury from electrical stimuli and by many chemical irritants produced the "triple response" which developed with the same time relations in all these forms of injury. It was probable, therefore, that it was brought about in the same way, namely by liberation of a chemical substance from the injured cells. Lewis brought forward much evidence for this conception and called the active intermediary H-substance because of its resemblance to histamine. He also showed that the vascular reactions of the skin in allergy and to the more slowly acting stimuli of ultra-violet light and X-rays, some bacterial poisons and chemical substances like mustard gas and cantharidin were fundamentally of the same kind.

The demonstration that histamine is a normal constituent of many tissues (Dale, Best, Dudley and Thorpe),<sup>2</sup> inactive so long as it remains within the cells but causing local vasodilatation when liberated, led Dale<sup>3</sup> to the view that Lewis' H-substance was histamine. The results which I shall now describe of perfusion experiments in which histamine was liberated by the action of physical and simple chemical means and by agents which cause shock-like conditions resembling anaphylaxis as well as by bacterial toxins and by animal poisons lend strong support to this conclusion.

In saline perfusion experiments histamine was estimated in boiled samples of perfusate and in saline extracts of ground-up portions of the perfused organs, by their immediate stimulant effect on pieces of the isolated jejunum of the guinea-pig in comparison with that caused by known amounts of histamine. That the substance so estimated was histamine was shown by the fact that titration by vasodepressant action on the blood pressure of the atropinised cat and sometimes by other pharmacological methods as well gave approximately the same values. In many experiments further evidence was afforded by the complete destruction of the active substance by histaminase.

THE LIBERATION OF HISTAMINE BY HEAT.—Rawlinson and Kellaway<sup>4</sup> perfused various isolated organs with saline at temperatures ranging from 37° to 50° C. in a lagged metal cabinet with a door fitted with a plate-glass window so that changes in the organ could

be observed. The temperature in the cabinet was controlled to  $\pm 0.1^{\circ}\text{C}$ . by means of steam distributed by a fan and the saline for perfusion was heated by passing through a water-bath maintained at the desired temperature to  $\pm 0.05^{\circ}\text{C}$ .

We first tried to find out whether anoxia associated with perfusion at temperatures above normal, in which tissue metabolism would be greatly increased, was itself a major influence in determining cell injury. We perfused the isolated lungs of guinea-pigs at  $45^{\circ}\text{C}$ . for 6 hours, ventilating the lungs with nitrogen and with air in alternate experiments. In nine pairs of experiments the mean output of histamine was 7.17 per cent. of the total store in the lungs when ventilated with nitrogen and 6.51 per cent. with air, but this difference was not statistically significant. In such lung perfusion experiments there was, however, one variable which is difficult to control. The products of cell injury are liberated into the tissue spaces and only appear in the perfusate when they are forced out by ventilation. Heat injury causes the lung to become immobile for a variable time, and the earlier this so-called "shock" passes off, permitting the elimination of oedema fluid, the larger is the total output of histamine. In a second small series of experiments in which stronger ventilation was used, we obtained about twice the percentage output of histamine we had observed in the earlier experiments whether the lung was ventilated with air, pure oxygen or nitrogen. It seems therefore that in perfusion with saline, anoxia is not the dominant factor in heat injury.

To ascertain whether the abnormal osmotic and hydrogen ion balance occurring in perfusion with saline at temperatures above normal might be the important influences determining cell injury we perfused the cat's liver through the portal vein at temperatures ranging from  $38^{\circ}$  to  $50^{\circ}\text{C}$ . Since these experiments lasted 9 to 10 hours they were carried out under aseptic conditions. After washing out the blood with sterile saline at a temperature of  $38^{\circ}\text{C}$ . the organ was set up in the cabinet, perfused at a rapid rate for long enough to bring the whole of the tissue to the required temperature and the perfusion rate was then reduced to 1 to 2 c.c. per minute. Such perfusion of the cat's liver caused swelling of the organ and the perfusate contained histamine in addition to pigment, protein coagulable by heat, inorganic phosphates and enzymes. These changes occurred in 2 to 4 hours at  $48^{\circ}\text{C}$ ., in 3 to 5 hours at temperatures between  $45^{\circ}$  and  $43^{\circ}\text{C}$ . and 6 to 10 hours at temperatures between  $40^{\circ}$  and  $38^{\circ}\text{C}$ .

In experiments at  $38^{\circ}\text{C}$ . injury was probably caused by autolysis and the output of cell constituents did not commence until after seven hours. At temperatures between  $40^{\circ}$  and  $42^{\circ}$  there was a more rapid increase in the rate of liberation of cell constituents than could be accounted for by the normal increase to be expected with rise of temperature in the process observed at  $38^{\circ}\text{C}$ .

We also observed the changes in pH of the perfusate and the effect of increasing the alkali reserve of the perfusion fluid by the addition



of sodium bicarbonate. By so buffering the perfusion fluid we were not able to influence the liberation of active substances at any particular temperature. It appeared, therefore, that in these perfusion experiments heat, rather than osmotic imbalance or change in hydrogen ion concentration, must be regarded as the dominant influence in causing injury.

We also perfused isolated limb preparations of the cat and guinea-pig and found that histamine was liberated at temperatures ranging from  $42.4^{\circ}$  to  $50^{\circ}$  C., but even in experiments at the same temperature there was much variation in the amounts liberated and in the time at which histamine appeared in the perfusate. These variations may have been attributable to opening up and closing down of capillary fields which made it difficult to keep the rate of perfusion constant.

**THE LIBERATION OF HISTAMINE BY RADIANT ENERGY AND BY PHOTODYNAMIC ACTION.**—Campbell and Hill,<sup>5</sup> extending the work of earlier observers, showed that dilatation of capillaries, stasis and emigration of leucocytes occurred in the tissues of living animal exposed to light, and Lewis' researches pointed to the liberation of a diffusible chemical substance as the cause of the delayed triple response in the human skin after exposure to ultra-violet radiation.

Trethewie, Holden and Kellaway<sup>6</sup> exposed the surface of the isolated lung of the dog perfused with saline at a slow rate to ultra-violet, visible and infra-red radiations for periods of from half to one hour and, despite the very small depth of tissue irradiated, found a definite output of histamine in the perfusate. After exposure to ultra-violet light there was a measurable loss of histamine from the store in the surface of the lung. These effects were due to the radiation and not to any local rise in temperature of the surface of the lung which was kept cool and moist throughout.

We also observed the effect of photodynamic action using protoporphyrin and hæmatoporphyrin as sensitisers. The severe circulatory symptoms caused by the exposure of sensitised animals to light must be related to injury of the skin and are probably caused by the release of histamine. The action of ultra-violet and visible light upon the lungs of dogs perfused with Tyrode solution containing one or other of these sensitising agents resulted in a much greater loss of histamine from the store in the irradiated surface of the lung than in their absence, but did not, when a slow rate of perfusion was used, cause the appearance of any more histamine in the perfusate than was produced by ultra-violet or visible light alone. We showed, however, that histamine is rapidly destroyed by photodynamic action and when we increased the rate of flow in the perfusions there was more histamine in the perfusate in the presence of sensitisers than was liberated by visible or ultra-violet light alone. Since histamine is protected by serum from photodynamic destruction it is unlikely that, in the intact animal, it is so destroyed within the body cells or tissue spaces. It must, therefore, be able to exert its full action in contributing to the symptoms of photosensitisation.

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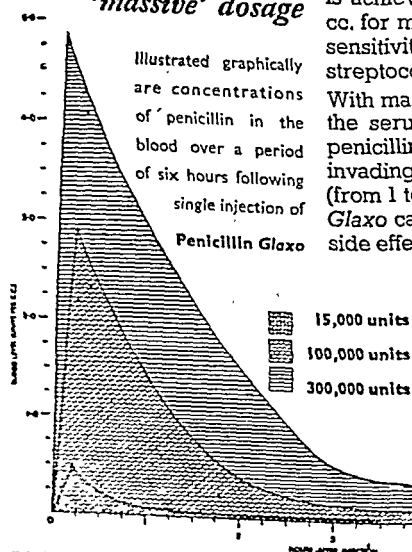
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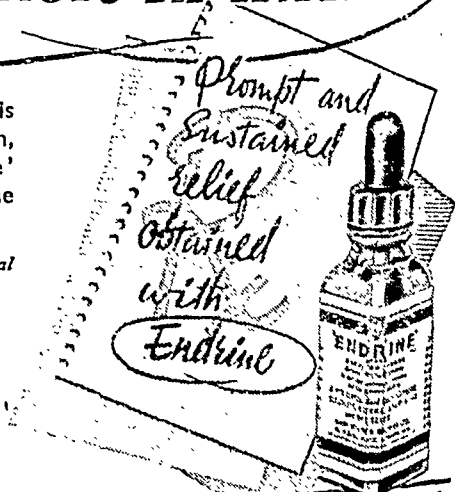
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**THE LIBERATION OF HISTAMINE BY A HEAVY METAL AND BY ANÆSTHETICS.**—We examined two kinds of injury caused by simple chemical substances—the effect of the salt of a heavy metal and that of volatile anæsthetics. Feldberg and Kellaway<sup>7</sup> injected mercuric chloride intraportally and intra-arterially into the perfused liver of the dog. This caused coagulative changes in the tissues and the liberation into the perfusate of histamine, as well as protein and pigments.

Chloroform, ether and ethyl chloride also cause the liberation of histamine from perfused tissues. It is interesting to recall that Dale<sup>8</sup> found that histamine shock was readily produced in cats anæsthetised with ether but did not occur when the anæsthetic was nitrous oxide. Trethewie and Kellaway<sup>9</sup> perfused the isolated lung of the dog ventilated with air containing volatile anæsthetics in varying proportions. Chloroform in concentrations over 4 per cent. for half to one hour caused severe injury to the lung with the liberation of histamine into the perfusate, but in the concentrations used for anæsthesia, 2 to 2.5 per cent, there was no evidence of such injury. The concentrations of ether used for anæsthesia, 5 to 16 per cent., just reached the level at which injury occurs and higher concentrations caused the liberation of large quantities of histamine. Ethyl chloride, in concentrations up to 20 per cent. for periods of half an hour or more, caused no detectable injury, but with higher concentrations histamine appeared in the perfusate. On the other hand, ethylene and nitrous oxide in concentrations up to 80 per cent. with oxygen caused no obvious injury and even when administered pure without oxygen caused the liberation of traces only of histamine.

Trethewie<sup>10</sup> later showed that chloroform injected intraportally in a dose sufficient to produce a concentration of the order of that occurring in anæsthesia caused the liberation of histamine from the liver of the dog perfused with saline.

**THE LIBERATION OF HISTAMINE IN ANAPHYLAXIS.**—The symptoms of anaphylactic shock in various species are strikingly similar to those produced in the same species by the injection of histamine. In the guinea-pig the dominant feature is bronchial constriction and in the dog injury to the liver which becomes intensely engorged, with hæmorrhagic congestion of the small intestine and a profound fall of systemic blood pressure. Dale,<sup>3</sup> in his Croonian lectures in 1929, showed that the hypothesis that histamine was liberated by interaction of antigen and antibody in the sensitised tissues fitted most of the observed facts. Not long afterwards Bartosch, Feldberg and Nagel<sup>11</sup> were able to show that, when the anaphylactic antigen was injected into the pulmonary artery of the isolated lungs of sensitive guinea-pigs perfused with Tyrode solution, bronchial constriction occurred and a substance, which was identified as histamine by pharmacological tests, was set free into the perfusate. These results were confirmed by Daly, Peat and Schild<sup>12</sup> who improved the perfusion method and recorded the changes in ventilation.

At about the same time as Feldberg and his co-workers made their observations on the guinea-pig, Dragstedt and Gebauer-Fuelnegg<sup>13</sup> observed that, in sensitised dogs, the intravenous injection of antigen caused the liberation of a substance which can hardly have been other than histamine into the lymph of the thoracic duct which drains the liver. Dragstedt and his colleagues<sup>14</sup> later showed that in anaphylaxis in the dog histamine was liberated in large amounts into the blood, and that there was a striking loss from the store of histamine in the liver. No one has yet demonstrated that the injection of antigen causes the liberation of histamine from the liver of the sensitised dog perfused with saline or defibrinated blood and it remains to be seen whether changes similar to those which have been observed after the injection of peptone determine the anaphylactic injury to the liver in this species.

In anaphylaxis in the rabbit the dominant features are leucopenia, fall of blood histamine and obstruction in the pulmonary circulation. The decrease in blood histamine can be explained by the disappearance from the circulation of the leucocytes which contain most of the histamine in the blood (Code<sup>15</sup>). Katz<sup>16</sup> found that if antigen was added to blood from the sensitised rabbit *in vitro* a considerable proportion of the cellular histamine was released into the plasma, and Dragstedt and his colleagues<sup>17</sup> perfused the lungs of the sensitised rabbit with the animal's own heparinised blood and found that, when antigen was injected, there was a striking reduction both in the total histamine and in the leucocyte count of the outflowing blood. If, therefore, leucocytes were concentrated in the vascular bed of the lungs and there, as a result of the reaction between antigen and antibody, liberated their histamine this would be able to act effectively on the lung vessels. It is interesting to note that only small quantities of histamine were set free into the perfusate when antigen was injected into the lung of a sensitised rabbit perfused with saline.

THE LIBERATION OF HISTAMINE BY ASCARIS EXTRACTS.—Rocha e Silva and his colleagues<sup>18</sup> have studied another interesting shock-like condition caused by the intravenous injection of extracts of the round-worm, *Ascaris lumbricoides*. In the dog this produced all the characteristic features of anaphylactic shock—congestion of the liver, loss of histamine from the store in that organ and increase in the amount in the circulating blood. As in anaphylaxis there is also incoagulability of the blood caused by the liberation of heparin. In perfusion of the dog's liver with Tyrode solution and even with defibrinated blood, highly potent ascaris extracts failed to cause any liberation of histamine; when, however, the liver was perfused with whole blood, citrated to prevent coagulation, the injection of ascaris extract caused a definite output of histamine and a striking fall in the leucocyte content of the blood. It seems by no means unlikely that this form of shock may be a genuine anaphylaxis, since dogs are

regularly infested with many intestinal worms, and may thus become sensitive either to the ascaris antigen or to those of other related worms.

**THE LIBERATION OF HISTAMINE BY PEPTONE SHOCK.**—The effects of the intravenous injection of peptone into the guinea-pig and dog were shown by Biedl and Kraus<sup>19</sup> to be closely similar to those of anaphylaxis. Lewis<sup>1</sup> observed that peptone injected into the human skin caused the characteristic triple response, and Dale<sup>3</sup> suggested that these effects of peptone, like those of anaphylaxis, were due to the liberation of histamine.

Further evidence in support of this view has been afforded by the demonstration by Feldberg and O'Connor<sup>20</sup> that histamine is liberated from the isolated lungs of the guinea-pig and cat perfused with Tyrode solution, the cell injury produced in the guinea-pig's lung by peptone and the amount of histamine set free being of the same order as in anaphylaxis.

Gotzl and Dragstedt<sup>21</sup> have recently shown that peptone shock and anaphylactic shock in rabbits are very closely similar since peptone causes a reduction in total blood histamine and leucopenia, and the addition of peptone to heparinised rabbit blood causes a rapid release of histamine into the plasma.

In the dog, when peptone is injected intravenously, histamine is liberated in large amounts into the circulating blood and into the thoracic lymph (Dragstedt and Mead<sup>22</sup>) and there is a striking diminution in the store of histamine in the liver. When the dog's liver is perfused with saline the injection of peptone causes the liberation of only small amounts of histamine, but as Rocha e Silva, Scroggie, Fidlar and Jaques<sup>23</sup> have recently shown, when the perfusion is carried out with whole blood without the addition of any anticoagulant (the glass in the apparatus being covered with a non-wetting film of silicone) enormous quantities of histamine, 3 to 8 mgms., were rapidly set free and with it even larger amounts of heparin.

The liberation of heparin in anaphylaxis and peptone shock is of importance in relation to the release of histamine. Heparin appears to give some protection in these forms of shock and in perfusion of the liver with heparinised blood peptone does not cause so much histamine to be set free as when no anticoagulant is used. The observation of the clumping of leucocytes and platelets in the vascular spaces of the perfused liver and their subsequent disintegration suggests that, in this form of shock, the participation of the whole blood is vital to the full development of tissue injury because of some intermediate action upon the leucocytes and platelets.

**THE LIBERATION OF HISTAMINE BY TRYPSIN.**—Crystalline trypsin, as Rocha e Silva<sup>24</sup> has shown, when injected intravenously into dogs and rabbits produces effects closely similar to those of anaphylactic shock. It causes the release of histamine from the isolated lungs of the guinea-pig and of histamine and heparin from the liver of the

dog perfused with saline. Histamine is also set free from the cells into the plasma when trypsin is added to rabbit's blood *in vitro*.

In the light of these facts Silva has put forward the interesting hypothesis that in anaphylaxis and in peptone shock a kinase is set free from the leucocytes or platelets and that this activates a proteolytic enzyme in the plasma which may be an important factor in the resulting cellular injury.

**THE LIBERATION OF HISTAMINE BY BACTERIAL TOXINS.**—Some bacterial toxins cause the liberation of histamine from isolated organs perfused with saline, significance being attached only to effects which are not produced in control experiments in which the toxic filtrates are neutralised with the corresponding antitoxins.

Toxic filtrates of *Staphylococcus aureus* in both the cat and rabbit cause, after a latent period of some minutes, a profound and fatal fall of systemic blood pressure due mainly to obstruction in the pulmonary circulation (Russ,<sup>25</sup> Kellaway, Burnet and Williams<sup>26</sup>). They cause the liberation of histamine from the isolated lungs of the guinea-pig and cat and from the lung and liver of the dog perfused with saline (Feldberg and Keogh,<sup>27</sup> Feldberg and Kellaway<sup>28</sup>).

Toxic filtrates from some of the gas gangrene anaerobes have also been examined including those of the four types of *Clostridium welchii*. These organisms produce at least ten toxins of which several are present in toxic filtrates from cultures of each type. Filtrate from type D, which causes an acute enterotoxæmia in sheep, liberates histamine from the isolated cat's lung perfused with saline (Kellaway, Trethewie and Turner<sup>26</sup>) and filtrate from type B, which causes lamb dysentery, also sets free histamine from organs perfused with saline (Kellaway and Trethewie<sup>29</sup>). Both these filtrates probably owed this action to the presence in them of  $\epsilon$  toxin. Filtrates from type A, one of the organisms which causes gas gangrene in man, and from type C, which is a pathogen in sheep, failed to cause the liberation of histamine in perfusion experiments. The result with toxic filtrate from type A was somewhat surprising because it contains  $\alpha$  toxin which Macfarlane and Knight<sup>30</sup> have shown to be a lecithinase. These experiments, and indeed all the experiments that have been made on the pharmacology of toxins of this group of organisms, need to be repeated using purified individual toxins in place of culture filtrates, experiments with which lose much of their value unless the culture filtrates are subjected to antigenic analysis (Oakley<sup>31</sup>) to ascertain what toxins are present in them.

**THE LIBERATION OF HISTAMINE BY SNAKE VENOMS.**—Tissue injury by snake venoms is more complicated than that produced by a single pure enzyme like trypsin. The venoms are a highly specialised form of saliva, and all contain more than one active constituent. Some venoms are coagulant containing an enzyme, which like trypsin, can convert prothrombin to thrombin or, like papain, act directly on fibrinogen converting it to fibrin. Some have an anticoagulant action.

Many venoms act dominantly on the nervous system, either centrally or peripherally, causing a curare-like effect on nerve endings in skeletal muscle. Some are hæmolytic and some cause local hæmorrhage and œdema at the site of injection or multiple hæmorrhages from damage to the small vessels. Most of our work was done with the venoms of the Indian cobra and Australian copperhead, which are anticoagulant, powerfully hæmolytic and neurotoxic. Feldberg and Kellaway<sup>32</sup> showed that both these venoms cause the liberation of large amounts of histamine from the isolated lungs of the guinea-pig and from the liver of the dog perfused with saline.

When venom was injected into the pulmonary artery of a guinea-pig's lung perfused with Tyrode solution, œdema of the lung occurred at once; the organ ceased to ventilate properly, and at the same time there appeared, in the perfusate, a heat-stable substance which caused an immediate histamine-like contraction of the isolated jejunum of the guinea-pig, a depressor effect on the blood pressure of the atropinised cat and a rise in the systemic blood pressure of the cat when directly injected into the arterial supply of the adrenal gland. All these different methods of estimation yielded approximately the same value in comparison with histamine for the amounts of active substance found in a given sample of perfusate.

We were able to show that the active substance in the perfusate was part of the store of histamine present in the lung. Extracts of the right and left lungs of the guinea-pig contain about the same amount of histamine, and when the amount of histamine in one lung was estimated and the other used for perfusion and injection of venom, the amount of activity estimated in the perfusate, together with the residual amount present in the lung at the end of the experiment, was approximately equal to that originally present in the organ.

Venom also caused the appearance of coagulable protein in the perfusate from the perfused lungs and when it was injected intraportally into the liver of the dog perfused through the portal vein, histamine, coagulable protein and pigments were set free into the perfusate.

In the cat and dog (Feldberg and Kellaway<sup>33</sup>) intravenous injection of either of these venoms caused a rapid and profound fall in the systemic blood pressure which, in the cat, was mainly caused by obstruction in the pulmonary circulation, and in the dog by peripheral vasodilatation, constriction of the hepatic veins and injury to the liver. In both species and with both venoms there was increased hæmoglobin concentration caused by loss of fluid from the circulating blood. The action of these venoms also resembled that of histamine in causing, in the dog, extreme congestion of the mucosa of the small intestine. This was accompanied by a prolonged increase in the lymph flow from the cannulated thoracic duct.

THE LIBERATION OF HISTAMINE BY BEE VENOM.—Bee venom caused symptoms in the cat and dog similar to those produced in poisoning by snake venoms and when injected intravascularly into



the perfused lungs of guinea-pigs and dogs and into the liver of the dog perfused through the portal vein it caused the liberation of histamine from these organs. In the dog it also caused prolonged increase in the lymph flow from the thoracic duct and changes in the mucosa of the small intestine like those caused by venoms and by histamine. Some histamine was regularly present in bee venom but when this was removed the venom still caused the effects which I have described.

In many of these perfusion experiments with snake venom, histamine was difficult to titrate because of the presence in the perfusate and tissue extracts of another active substance or substances which caused a delayed slow contraction of the isolated guinea-pig gut preparation which relaxed only slowly when the Tyrode solution was changed. The contraction was followed by characteristic after-changes in the sensitivity of the gut to histamine or acetyl choline. There was first an increase, then a gradual decrease and finally in the course of ten to twenty minutes, return to normal sensitivity. When we perfused the liver of the monkey, which contains but little histamine, we found that, after the injection of venom, though there was no appreciable liberation of histamine, the perfusate regularly contained this other active substance. In extracts of untreated liver it was either not present or present only in traces, and we therefore concluded that the substance or substances must be formed by the action of the venom (Feldberg and Kellaway<sup>34</sup>).

The venoms which were most active in causing the liberation of histamine and the formation of this slowly-reacting substance were powerfully hæmolytic. It seemed possible, therefore, that the injury caused by venoms to tissue cells might be of the same nature as their action on red blood corpuscles. Venom hæmolysis was known to be enhanced by lecithin and Delezenne and Fournau<sup>35</sup> had shown that cobra venom splits off a molecule of oleic acid from lecithin and forms lysocithin which is itself actively hæmolytic. It was conceivable that the formation of lysocithin might be an intermediate step in injury to the cells by venom and that our "slowly-reacting substance" might be formed by the action of venom on cell lipins.

Holden<sup>36</sup> prepared lysocithin by the action of venom on egg lecithin and freed it from the contaminating slowly-reacting substance and from venom, and though he could not isolate slowly-reacting substance in a pure state he made preparations which were active in a dose of 1 mg. and were free from venom and lysocithin.

Feldberg and Kellaway<sup>36</sup> found that lysocithin closely resembled cobra venom in many respects. When injected intravenously into the cat and dog it caused a steep fall of systemic blood pressure which in the former species was associated with a rise of pressure in the pulmonary artery and hæmorrhagic œdema of the lung, and in the latter with a rise of pressure in the portal vein. It caused contraction of the isolated uterus of the guinea-pig and peripheral vasodilatation when injected into the femoral artery of the dog. It caused the

liberation of protein, pigments and histamine from the perfused liver of the dog and of protein and pigments from the perfused liver of the monkey.

Lysocithin differed from venom in that the perfusates from the dog's liver after its injection contained only small amounts of slowly-reacting substance, and in those from the monkey's liver none could be detected. It hæmolysed sheep erythrocytes and decreased the excitability of the isolated jejunum of the guinea-pig.

**SLOWLY-REACTING SUBSTANCES.**—S.R.S. can only be recognised by their action on smooth muscle and we have no evidence that they have any other pharmacological action. The reaction of the isolated jejunum of the guinea-pig to a first dose of venom, peptone, trypsin and of some bacterial toxins and the anaphylactic response of the sensitised smooth muscle to the antigen all display slow relaxation and after-effects of the same kind. It is possible that the formation or liberation of S.R.S. plays a part in the contraction of smooth muscle produced by some of these agents.

No S.R.S. are either formed or liberated when tissue cells are coagulated by heat or by a mercuric salt nor do they appear in injury by ultra-violet, visible or infra-red radiation nor in the photodynamic injury. The  $\epsilon$  toxin of *Clostridium welchii* failed to liberate them nor were they set free by the  $\alpha$  toxin (lecithinase), but they appeared in the perfusate from the isolated liver and lung of the dog when a toxic filtrate of *Staphylococcus aureus* was injected though there was no evidence of the simultaneous formation of lysocithin (Feldberg and Kellaway<sup>7</sup>). They also appeared in the perfusate from the dog's lung when it was ventilated by high concentrations of chloroform, ether and ethyl chloride and in that from the perfused liver of the dog after the intraportal injection of small doses of chloroform (Trethewie<sup>10</sup>). Trethewie<sup>37</sup> has also shown that S.R.S. is liberated from the perfused liver of the rabbit by the injection of trypsin.

Of special interest is the liberation of a substance of this kind in anaphylaxis. Trethewie and Kellaway<sup>38</sup> found it, after the injection of antigen, in the perfusate from the lungs of sensitised guinea-pigs perfused with Tyrode solution. In extracts of the perfused lung and intestine of sensitised guinea-pigs after the arterial injection of antigen or after incubation of the ground-up tissues with antigen it was present in greater amounts than in the same tissues extracted without contact with the antigen. When sensitised tissues were ground up and dried before extraction the content of S.R.S. in the extracts was greater than that of fresh saline extracts of the same tissues and there was no increase in the yield of S.R.S. when dried sensitised tissues were incubated with the antigen. This was in striking contrast to the large increase of S.R.S. which was formed when dried tissues were treated with snake venom. We concluded that in anaphylaxis the substances with this action were set free from the tissues and not formed as in tissue injury by snake venom.

Incidentally there is no evidence that the substances with this action which are set free from the tissues in anaphylaxis, by trypsin, by staphylococcal toxin and by volatile anæsthetics are identical with the substance formed by the action of snake venom on the tissues and on egg lecithin.

**MENKIN'S LEUKOTAXINE.**—The evidence which I have presented concerning these various types of tissue injury lays increasing emphasis on the part played by histamine. We should at this point discuss the interesting studies of Menkin<sup>39</sup> who has obtained from non-infective inflammatory exudates several active fractions which are of importance in the more slowly developing phenomena of inflammation. One of these, leukotaxine, is of especial interest. This is a heat-stable, dialysable polypeptide or mixture of polypeptides which, when injected into the skin of the rabbit, causes trypan blue (injected intravenously) to accumulate at the site of the intradermal injection and has an active chemotactic effect upon the leucocytes. Menkin<sup>40</sup> showed that a substance or substances which behaved similarly could be formed by the action of proteolytic enzymes on serum proteins.

Cullumbine and Rydon<sup>41</sup> have recently observed that a substance producing these effects is present in extracts of normal skin and in larger amounts in extracts of skin thirty minutes after injury by heat, mustard gas or lewisite and that it can be formed directly by the action of mustard gas on serum and by proteolytic enzymes like the proteinase shown by Peters and Beloff<sup>42</sup> to be set free from skin by thermal injury. There is no evidence that it is a normal cell constituent. It is unlikely that it can contribute to the "triple response," but it is formed early enough and in sufficient amount to play a part in the development of vesication in thermal and chemical burns. Menkin<sup>39</sup> thought that leukotaxine must be responsible for the alteration in permeability which results in the accumulation at the site of injury in the skin of the rabbit of trypan blue injected intravenously since histamine in the large doses which he used, 0.1 to 10 mg., gave a central pale area surrounded by a blue halo. Rocha e Silva and Dragstedt<sup>43</sup> have, however, shown that this phenomenon is seen only with large doses of histamine and of substances which are known to cause its liberation, whereas doses of histamine of the order of 0.5 to 2  $\mu$ g. cause a diffuse accumulation in the area round the injection like that produced by "leukotaxine." Whether the effect of "leukotaxine" in causing the increase of permeability of the capillaries is a direct one or indirect by the local liberation of small amounts of histamine still remains to be decided.

**CARDIO-DEPRESSANT ADENYL COMPOUNDS.**—A striking feature of the action of cobra venom on the heart of the dog, cat and rabbit, as evidenced by electrocardiograms in the intact animal, is impairment of conduction between auricle and ventricle. In the rabbit, for example, Trethewie and Kellaway<sup>44</sup> observed bradycardia, increase in the P.R. interval and terminal heart block after the injection of cobra venom.

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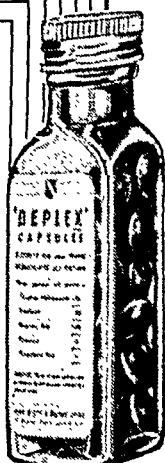
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These changes were not attributable to any gross lesions in the heart or coronary vessels though in this species constriction of the coronaries may contribute to them. Nor are they attributable to asphyxia, since the blood was kept well oxygenated by artificial respiration. They cannot be explained by the low level of systemic blood pressure for they were not observed in rabbits in which a level of blood pressure of from 10 to 30 mm. of mercury was maintained by bleeding. They cannot be attributed to the local action of histamine and it seemed likely that some other active substance was set free by the venom, either in the heart itself or in organs from which the venous return quickly reached the heart.

Drury and Szent Györgyi<sup>45</sup> attributed the depressant effects on the mammalian heart of the injection of extracts of heart muscle and other organs to the action of adenylic acid which slows the heart rate and impairs conduction, and Drury and his colleagues<sup>46</sup> devised a method by which, in the atropinised guinea-pig, solutions containing adenylic compounds might be titrated for their cardiodepressant effects in comparison with adenosine or adenylic acid by injection into the left auricle, a record being made of the contractions of the right auricle.

When cobra venom was injected intraportally into the isolated liver of the rabbit and into the aorta of the heart of the cat perfused with saline large amounts of active cardiodepressant substances were liberated into the perfusate and with them a heat-labile agent which rapidly inactivated both the perfusate and adenosine even at room temperature. The test animal was protected from the action of the venom by passive immunisation with antivenine. Lysocithin, which is also cardiodepressant and heat-stable, was not present in sufficient amounts to interfere with the titration.

We were able to prevent losses of activity during collection by allowing the perfusate to fall directly into vessels immersed in boiling water and as each sample was collected brought it to the boil to destroy any enzyme present. In some experiments we perfused the organs with sodium cyanide which inhibits the inactivating enzymes within the vessels of the perfused organ, and were able to show that almost the whole of the difference between the activity of extracts of perfused liver before the injection of venom and at the end of the experiment could be accounted for by cardiodepressant substance estimated in the perfusate, whereas if these precautions were not taken the amount estimated in the perfusate was much less than the total loss from the organ.

The rabbit's liver is rich in active adenylic compounds but they are not set free during perfusion for an hour or more with Tyrode solution nor is any inactivating enzyme liberated. When, however, a small dose of cobra venom was injected intraportally from 50 to 80 per cent. of active substances present in the tissue were set free within an hour, most of it within the first ten minutes after the

injection of venom. Lysocithin also caused an immediate, though transitory, liberation of active cardiodepressant substances from the liver.

The injection of 1 mgm. of cobra venom into the perfusion cannula of the actively beating perfused heart of the cat caused cessation of the beat in about two minutes and at the same time active cardiodepressant substances appeared in the perfusate in considerable amounts, although they could not be detected in the outflowing fluid before the injection of venom. Lysocithin injected into the perfusion cannula also caused cessation of the heart beat and the liberation of cardiodepressant substances in the perfusate. It is of interest that the cessation of the beat caused by asphyxia did not cause the appearance of any of these compounds in the perfusate.

In the terminal stages of poisoning with toxic filtrates of all types of *Clostridium welchii* in various species impairment of conduction manifested by prolongation of the P.R. interval and heart block is of frequent occurrence. All these toxic filtrates when injected intraportally into the liver of the rabbit and into the aorta of the heart of the cat perfused with saline caused the liberation of heat stable cardiodepressant compounds. From the liver there was also set free a heat-labile agent which readily inactivated both adenosine and the depressant substances in the perfusate (Kellaway and Trethewie,<sup>29</sup> Kellaway, Trethewie and Turner<sup>28</sup>).

In injury of the liver by chloroform in concentrations at about the same level as occur in anaesthesia, Trethewie<sup>10</sup> has shown that similar actively cardiodepressant compounds are set free from the perfused liver of the dog together with an enzyme which can inactivate them. In injury by trypsin, adenyl compounds and inactivating enzyme are liberated from the liver of the rabbit perfused with saline (Trethewie<sup>37</sup>).

The question as to whether in tissue injury by heat actively cardiodepressant substances are liberated is of particular interest in view of the recent researches of Green and his colleagues<sup>47</sup> concerning the significance of adenosine triphosphate and related compounds in the pathogenesis of shock.

In perfusion of the isolated limb preparation of the cat and guinea-pig with saline at various temperatures between 42° and 50° C., Rawlinson and Kellaway<sup>4</sup> were unable to demonstrate the liberation of any cardiodepressant compounds which could be inactivated by the deaminating enzyme which is present in fresh extracts of muscle and liver. Our results were still disappointingly negative when cyanide was added to the perfusion fluid and when relatively fast rates of perfusion were used. It seems unlikely that in heat injury such adenyl compounds play any important part in causing cardiodepressant effects because of the extreme activity of the deaminating enzymes present in the blood and tissues. But as Green has suggested deamination may result only in the loss of their cardiodepressant activity

and they may, like inosine triphosphate (the residue after deamination of A.T.P.) still be capable of playing a part in the genesis of shock.

The results of the experiments we have discussed illustrate the usefulness of the perfusion method in the study of tissue injury. They also disclose its limitations, particularly when saline is used as the perfusion fluid. In injury by peptone, perfusion with whole blood without the addition of anticoagulants is necessary in order to produce in the isolated liver of the dog injury comparable to that which occurs in the intact animal. This is probably also true of injury by trypsin and by ascaris extracts and it seems likely that in all the conditions closely allied to anaphylaxis and in anaphylaxis itself the full development of the process of injury in isolated organs will prove to be possible only when blood is used as the perfusion fluid. In injury by some bacterial toxins perfusion with whole blood may also prove to be the most satisfactory method of reproducing in isolated organs the degree of injury observed in the intact animal.

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## SOME PROBLEMS IN ASSESSING THE PART OF TRAUMA IN NERVOUS DISEASE \*

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IN considering this subject it is necessary to impose definite restriction on the scope or width of those aspects selected for the purpose of discussion. Without such limitations one is apt to become too diffuse and to be submerged in a deep sea of one's own creating. Definitions and clear thinking are essential. The title is worded to indicate that it is my purpose to consider trauma as an etiological factor in determining or aggravating a nervous disease or morbid process, and to exclude those accidents and injuries the effects of which are plain for all to see; a lacerating wound of the head, a fractured spine, and many other similar results of violence. My motive is to focus attention on cases in which the possibility of trauma has to be considered as a possible factor. As we are all aware this is a problem often beset with difficulty. One which in law has too frequently caused doctors to resemble clowns, displaying the same self-importance, the same inability to see each other's point of view, the same apparent anxiety to help with the urge to obstruct, reminiscent of delegates to the Assembly of the United Nations. What is the reason for all this? Differences of opinion expressed by medical men are often, indeed usually, due to the differences in the interpretation of the facts, in knowledge and judgment, expressed rather neatly in Clark Kennedy's *The Art of Medicine in Relation to the Progress of Thought*: "Science looks for a definite answer to a general question, medicine demands judgment in a particular case." That is the difference. Again and again in our present state of knowledge, we find ourselves adopting Kant's definition of faith—"holding something to be true on grounds sufficient for action, although they may not be altogether sufficient to satisfy the intellect."

Nowhere in the whole field of medicine is there greater need for balanced judgment than in assessing the rôle of trauma in nervous disease. It is so easy to be partial or biassed, to favour this view or that, when in reality what is most required is a careful appraisal of facts.

This subject has interested me for many years, and one can claim a considerable experience, both in civil and military practice. In this period of post-war turmoil there is greater need than ever for practitioners and specialists alike to take stock of the position, and determine at least the broad principles of their attitude when confronted with this problem of trauma in the individual case. "The death rate is a fact, all the rest is inference," said William Farr, which is true only in so far as opinion is concerned, but it does serve to remind us

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of how permanent are the facts in a given case—the inference, or assumption, can only be based on the facts, and therefore become a matter of judgment. Opinion would be simple if the facts were invariable and capable of measurement. If this were so, our calling would be intolerable. But many of the facts, so-called, are based on statements, we are still free to sharpen our wits by training and experience, and so it comes about that in the same case doctors differ. Again it is to be remembered that the knowledge and experience of medical men vary greatly as does their judicial faculty; this aspect I shall have occasion to mention later.

Before proceeding further it is well to consider the precise meaning of the word "trauma." As Dr Joad would say, "What exactly do we mean by trauma?" The *Oxford Dictionary* defines trauma as "a wound or external injury in general, also the condition caused by this," a typically subtle use of words, elastic but controlled. In medicine we take advantage of this and use the word trauma when applied to the nervous system with a somewhat wider application than this definition MIGHT seem to imply. We sometimes speak, for instance, of a "mental trauma," as for example, a terrifying or distressing incident or a sudden bereavement, and the "nervous," mental or emotional effects which may result. Just as in the sense we speak of a mental collision when in fact we do not infer any actual violence but rather the state of mind in, say, the motor driver approaching the traffic lights when he oscillates his foot between accelerator and brake. In this connection we have to deal with human personality and human hopes, fears and feelings in conjunction with the material human body which is exposed to so many disasters in the physical environment of our existence.

Realising that most of you probably have unique experiences of your own I propose to take up quite briefly four aspects of the subject:

(a) Physical trauma as an etiological factor in the determining or aggravation of nervous diseases.

(b) Cases in which physical trauma and associated mental trauma, a consequence of the environment at the time the trauma is received, produces perhaps comparatively slight if any organic damage, but pronounced functional manifestations, *i.e.* nervous, mental or emotional symptoms.

(c) Cases in which functional manifestations persist or on the other hand are originated, and it may be perpetuated, by the fear that return to work may result in a relapse when no compensation may be received, or fear of the return to the surroundings in which the accident occurred, or ideas regarding compensation (determined by his doctor who is afraid to express a dogmatic opinion, or by an unscrupulous lawyer), or if his case comes to court (when he is permitted to hear the evidence) by the opinion of medical witnesses called by the opposing lawyers who, he believes, have been paid to express the opinion that he is fit for work or should make a speedy recovery.

(d) The estimation of exaggeration and the detection of cases of malingering.

TRAUMA IN ORGANIC DISEASE.—In one group the evidence is clearly such as to make the relationship beyond all doubt; these instances in which the injury and nothing else is entirely responsible for the subsequent clinical state. These need not detain us, as any controversy must only centre round the amount of compensation to be awarded.

Many well-recognised nervous entities have been alleged from time to time to have arisen as a result of an accident or injury, often the association as described is at least suggestive, but no less often the relationship in time is so remote as to make the connection highly improbable, indeed one has learnt to respect this time factor in inverse ratio to its length. A point which the lay mind is very ready to accept. Sooner or later in the practice of every medical man a case arises in which the possible rôle of accident in determining the onset of disease becomes a major pre-occupation. What have we to guide us in our judgment? The literature in all countries abounds with examples, and the reviewer quickly recognises a bias for or against, according, it will seem, to the individual author's samples, necessarily a limited and variable cross section. Yet when confronted with a particular case certain established principles do emerge to guide us. We have the nature of the accident and the time factor, what is known of the etiology in the disease that develops subsequently, but above all a careful consideration of the accepted pathology enables a reasonable inference to be arrived at in the judgment of a given case. Quite recently in another place I took up this aspect of the subject in some detail so do not propose to repeat myself, but will select briefly a few typical examples from current experience to bring out the salient features in this group.

An analogy worth remarking is the long recognised fact that in a textbook the larger the number of methods of treatment mentioned the less likely is any one line to be specific; so it is in regard to etiology when we see trauma tucked away among such diverse possibilities as exposure, infection, shock. Yet in scarcely a single organic disease whose cause is unknown can we not find theorists who have speculated in this relationship through the years until, and this is important, a definite etiological factor has been worked out. After this silence has been the rule in regard to trauma. Consider neuro-syphilis and disseminated sclerosis. In the former the causal organism is beyond dispute so speculations are ruled out, whereas in the other fascinating conjectures are constantly entertained and are likely to continue until truth emerges. If we believe, as we should, in prime causes, then history is sufficiently suggestive to cause extreme wariness in apportioning an injury or accident as a selective cause of organic disease. Yet it happens not infrequently that the coincidence of violence is so exact as to appeal readily to the mind of laymen and less expert doctors

alike. A young woman received a painful blow on the left knee and two weeks later unmistakable signs of disseminated sclerosis were found in a routine examination—or the case of a fireman who slipped down a long flight of stairs in a sitting posture, receiving thus fourteen bumps which jarred the spine, and in whom, when examined two weeks later a fully developed picture of disseminated sclerosis was present although the patient stated that he was perfectly well before the accident. In these and similar cases the trauma would, to the layman and the inexperienced clinician, appear to be the factor which originates the disease; on the other hand we know from accumulated experience that trauma is a factor which very rarely arises in the etiology of this disease, that, in the cases referred to, evidence of disseminated sclerosis would have almost certainly been detected had the patient been examined before the accident. There is, in fact, no evidence to show that trauma is ever the actual cause of disseminated sclerosis, although it may be an aggravating factor.

During the second half of last century, when disease was laboriously being classified on a clinical basis, it must often have been amusing to advance etiological theories of one sort and another, knowing that few contemporaries could have gathered sufficient clinical material as to offer serious rejection. However this classification was concluded many years ago, and as its sequel has come, with extensive statistical studies, the opportunity for precision which should cause us to deplore, without necessarily being aloof, arguments based on the viewpoint of fifty years ago. Facts there are now in abundance, some perhaps not indisputable, but sufficient and all aggregating to disprove the rôle of trauma as the prime or essential causes of distinguishable maladies such as disseminated sclerosis, progressive muscular atrophy, cerebral tumour and Parkinsonism. Even in such cases, relatively rare, in which a reasonable element of doubt might exist, we must, as medical men, be as dogmatic as the available evidence permits, but not impair our reputation by overdogmatism.

By now my audience must have thought of epilepsy and wondered if I had forgotten. Here, of course, the case is different, coming almost into a category of its own, for an epileptic fit is a symptom and not an entity like those just considered. That is to say that it is a condition for which many and diverse etiological factors may exist, or even co-exist, and moreover such factors are frequently capable of proof, again unlike cerebral tumours and the others. It seldom happens that a man who suffers head injury develops convulsions, but, if the boy who was hit on the head by a bottle during a riot in Trieste, takes his first major fit within a very few weeks, we only require to establish a completely innocent antecedent history to convince ourselves, and all others, of the connection between the two events—the bottle and the fit. We know from experience of numerous similar cases that this man's claim for a pension will receive a favourable decision as it would have done had it been an industrial accident. The two episodes



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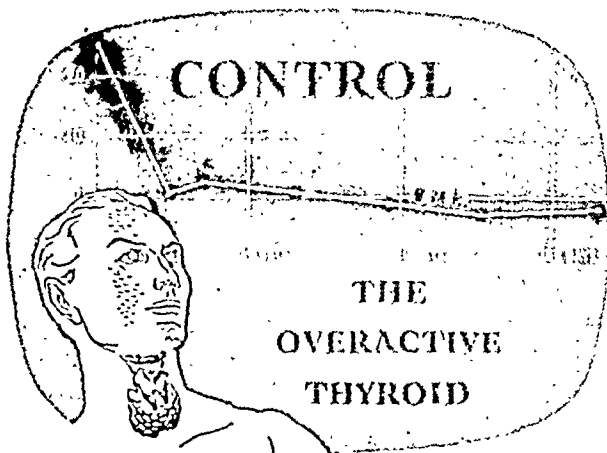
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hang together in reasonable relationship in a person with an unblemished medical record. Even so we must still ask ourselves why it occurred in this particular case. If head injury was constantly followed by epilepsy the answer would be simple, but we know that it is the exception rather than the rule otherwise the epileptic population would be colossal. Is it not that in a single instance the violence is but a predisposing cause, meaning that it is added to something else which already exists, a something that has made him more susceptible? We must visualise a group of "silent" epileptics who may slip through life with no fits, but who are at the mercy of such a predisposing cause. Sometimes they are easy to detect, as when the family history is suggestive, but more often they are unsuspected. Perhaps Hurst's percentage of peptic ulcer subjects is an analogous story.

The experience of two major wars has proved beyond any doubt that trauma has merely been the last straw, determining a fit in a relatively small number of individuals whose constitutional make up had made them candidates. How otherwise could we explain that out of many thousands of head wounds and injuries only a small minority, after the lapse of even some years, became epileptic? Here is an instance of where precise statistical information should be made readily available to every medical man for his due consideration and digestion before appearing in court to give evidence about a single case, thus contributing towards that medical doctrine that would be so desirable. Such a catalogue of reliable information, supported by unbiassed and unimpeachable statistics, must be built up slowly, and I can think of no more suitable starting point than epilepsy since the available figures are enormous and impressive.

Thus far I have considered trauma in its possible relationship to nervous disease, entities whose nature is either understood in whole or in part and it is seen that the more the true etiology has been elucidated the less the likelihood of injury playing any important part, let alone the only rôle. Yet in the whole field of organic nervous disease there is a group of conditions in which it may be claimed to occupy a place no less definite and specific in its way than a pyogenic or virus infection in their particular sequels. But before considering this it is necessary for me to define the meaning of the word more carefully to avoid misunderstanding of the sense implied. Hitherto in the sense used an external injury has been understood, a violence primarily to the surface of the body, but in our very mobile and flexible skeletons it is possible to visualise a state of affairs in which nervous tissues, ordinarily protected by bone, become damaged by an alteration in relationship of such protection due to wear and tear, loss of weight, change of shape, or posture, twists, jerks or similar disturbances. To this it seems proper to use the term internal trauma collectively, since in the first instance the effects are brought about by movement which makes it differ only in degree from the type of trauma more commonly thought of and already discussed. Lest it be thought that



I stretch credulity too far let me point out that this has for long been the happy hunting ground of osteopaths and chiropractors who owe what success they have entirely to the relief of pain; indeed were it not so none of these people would survive in business for a week.

We are all familiar with the palsy which results from compression of a radial nerve, the so-called crutch palsy or drunkards' palsy, resulting in a variable weakness of the extensor muscles at the wrist, clearing up in a matter of hours or days. Rapidity of improvement bearing a direct relationship to the shortness of compression; an association that has long been recognised and indeed precautions taken to avoid as in the positioning of a patient's arms during an operation. The lesson of this may with benefit be applied to other situations in which a single peripheral nerve shows altered function. A middle-aged woman saw me recently, complaining of pain, numbness, and a tingling sensation running down the right arm from the shoulder to the ulnar fingers, increasing during the past six to eight weeks. She gave a history of long continued drudgery in her home, with family, cooking, washing, etc. Her appearance was striking and suggestive with obvious pallor and a drooping, tired look, but the only physical sign was the slope of her shoulders and tenderness on pressure above the inner third of the clavicle and over the transverse process of the seventh cervical rib. Objective sensation down the arm was quite normal, and no muscular wasting or weakness existed. Since the beginning of the last war this condition has become widespread, and one sees it most frequently in females, although males are by no means exempt. Manifestly it merits the title of syndrome, the syndrome of acroparasthesia, a condition in which repeated microtrauma over a normal first thoracic rib is the incident which draws attention to the general background of poor health and altered posture. In younger women a history of recent childbirth or the care of a child appear to be frequent precipitatory factors. The onset is gradual and at first occasional bouts of numbness, pain or tingling appear chiefly in the distribution of the ulnar nerve, and often at the end of a hard day's work. The symptoms may be particularly prominent in the digits and lead to clumsy finger movements. Heavy work aggravates it and curiously these patients, at least in the early stages, sometimes say that the time of greatest disability is in the morning. After some months, as a rule, the symptoms become stationary at a certain level of severity and tend to fluctuate. A carefully taken history will frequently elicit the fact that any holiday has been followed by a marked remission of symptoms, the condition relapsing again; as often as not symptoms are complained of on both sides.

I adjudicated a few weeks ago in favour of an A.T.S. girl of 24 whose main complaint was of numbness and tingling in the arms keeping her awake at night. It transpired that several months previously she was transferred from office work to employment in the kitchen preparation room, involving heavy lifting and much manual

work. Examination confirmed the syndrome as described with a low set shoulder, and the line of the clavicle almost horizontal, although this point by itself is not diagnostic as it is seen in some normal persons. Tenderness may be marked in the muscles of the forearm and also in the hand, and I have seen cyanosi and pallor of the fingers occasionally, also weakness of the grip may be suspected but pain and tenderness interfere with the test.

The etiology of this condition has long been a matter of speculation, but Walsh (1945 *B.M.J.*) in a forceful article has re-emphasised the importance of the topographical relationship of the shoulder girdle to the upper thoracic outlet. He points out that the striking complaint of these patients is of fatigue and debility with a history of heavy use of the arms and great relief of symptoms after holidays. His belief, supported by convincing reasoning, is that in the great majority of these cases the shoulder girdle has dropped in relation to a normal upper thoracic outlet and this causes repeated small trauma on components of the brachial plexus as they pass over a normal first thoracic rib. Further support for this is the fact that the syndrome tends to occur later in life when, as is well known, the dropping of the shoulder girdle is extremely common.

All of us are familiar with the neuritic manifestations of vitamin deficiency, metallic poisoning such as lead and arsenic infection or intoxication like diphtheria or infectious polyneuritis, even diabetes. A moment's reflection recognises one feature common to them all, namely, their uniformly bilateral nature. Is it possible then that a single nerve or components of a plexus on one side only can be influenced by these agents. From long observation of such conditions my considered opinion is that, while predisposing factors may co-exist, the underlying determinant in a one-sided lesion has been the weakening of the nerve by internal trauma. This case is typical of many :—

A senior officer suffered acute brachial neuritis on the right side, with tenderness and some weakness and wasting in the proximal part of the arm. He had done much desk work in a cramped writing position over many months. Routine investigation discovered an apical abscess in a molar of the same side which was extracted, but the condition lingered on until his posture was corrected first by elevation of the shoulder, and later exercises designed to increase the space between the clavicle and first rib. It must be allowed that either the abscess or the pressure could have produced the effect alone, but how much more probable that the two were interdependent.

Several authors have remarked upon the greatly increased incidence of "idiopathic" neuritis seen during the war years. Such causes as intoxications and deficiency states are claimed to have been eliminated, and it is often believed, without much evidence, that the condition may be the result of virus infection. But here again the rôle of trauma, which I regard as so important, has either been slurred over or omitted altogether, notwithstanding the remarkable fact that the very nerves

implicated are the ones most vulnerable to altered bony relationship. As an indication of its partly mechanical nature one patient of mine had no fewer than three relapses until steps were taken to alter his postural defect. The undoubted character of this idiopathic type of neuritis does not absolve the practitioner from excluding other lesions, and at one stage it may closely resemble poliomyelitis, both conditions tending to occur in the limited age group met with in service practice. An initial error is soon corrected by subsequent events. A number of these cases are reputed to be associated with the giving of preventive serum, but here again it surely cannot be more than another item in the train of events.

Work for the Ministry of Pensions now adds greatly to the duties of medical men, and a clear understanding of the implications of "neuritis" is more necessary than ever if we are to discharge our task honourably and intelligently. Here again it is an aspect of nervous disease most suitable to be listed in a journal of medical doctrine. Until this happens a large body of independent medical opinion will continue to be ignorant and variably biassed, having no "ready reckoner" to guide them in what must often be an isolated experience in a busy family practice.

As illustrating a sequel where trauma is an undoubted determinant in nervous disease let me cite a puzzling example of a few days ago: A skilled labourer of 56 was descending iron ladders in the rain while carrying a pail on his left shoulder when both feet slipped and he supported himself by instinctively clinging by a strong right grip, thus twisting his body forcibly. Regaining control he descended, but experienced a sharp pain between the shoulder blades. Three days later he was back at work feeling only a dull ache, and for over a year pain troubled him in this situation only intermittently, lasting for hours or a day or two when he made a sudden unexpected movement, but never severe enough to keep him off work until, a month ago, he lifted a heavy box when pain became severe. Ensuing rapidly he has had unsteadiness, followed by progressive weakness of both legs, numbness and bladder dysfunction until soon he became bedridden. Examination was not long in placing the anatomical site of the lesion at the 6th dorsal segment of the cord, its pathological nature requiring further consideration. An X-ray showed an eroding lesion of the body of the 6th thoracic vertebræ. With lumbar puncture Quickenstedt's test was positive, and the B.S.R. performed three times at intervals has averaged 130 mm. in one hour.

A diagnosis in this case can only be reached by a careful evaluation of the time factor in the history which is the very essence of the problem. Is the original twist alone responsible by itself, or with some additional feature? Can the jerk and the subsequent pathological process be dissociated? Did the slip hasten the development of a new growth which was destined to occur at any rate? The other possibility, suggested by the radiologist, of a metastatic tumour is ruled out by

an absence of signs of the necessary primary. Judgment in a given case depends on many factors, but not least on clinical experience. The initial history in this instance is fully compatible with a partially herniated intervertebral disc, and so it is not too much to assume a subsequent inflammatory exudate with a finally developing infection, all of which would explain the compression paraplegia and exceptionally high B.S.R. The question of herniated nucleus pulposus is of first and lasting importance. The example given happens to be an industrial accident, and happens also to be in a less usual situation in the spinal column, the lumbar and even cervical regions being much more frequent; but it does illustrate something of the scope of the problem and indicates too the more physical outcome. At the other end of the scale, he who stubbed his foot in a hole and thereafter had constant low back pain, diagnosed eventually as a neurosis to the extent that he was an inmate of a mental hospital at the time the true diagnosis was established. This case ended happily in so far as the man made a complete recovery both physically and mentally.

This lesion has been most frequently referred to in the literature as "Herniation of the Nucleus Pulposus," "Protrusion of the Intervertebral Disc," "Rupture of the Intervertebral Disc." None of these commonly used headings clearly identify this syndrome which has now become firmly established as an irritation of a spinal nerve caused by an *injured* intervertebral disc. It has been proved that many times the nucleus pulposus is not herniated and often the disc does not protrude in this disorder. Rupture of the intervertebral disc is a more accurate pathological designation, but does not include the major manifestation of this disorder—the spinal nerve pain. Clinically it is often difficult to distinguish the disc syndrome from sciatic neuritis when the process occurs either in the roots of the nerve or in the trunk of the nerve itself. Indeed it is probable that trauma, either major or repeated minor, is responsible at least in part for the neuritis here just as in the case of brachial neuritis.

What are the special points that must be brought out in the clinical examination of a case which would make the physician suspect that a disc protrusion is present? A study of the literature makes it clear that opinion is very divided on this question, so that one is best guided by personal experience. The type of onset is important—the patient who had an accident and injured his back a few months ago and quite suddenly developed severe backache two or three days ago, which went into his leg the next day is a likely type. It suggests a rupture of the disc especially if the pain is very severe and he can hardly move in bed. A history of recurrent pain in the back with intervals of complete freedom is suggestive, more especially if it appears that on one or more occasion the sciatic pain disappeared suddenly. This is almost pathognomonic of a disc. The age of the patient is of little help, the young man is supposed to have a protrusion because he is a harder worker, more likely to suffer trauma and for no other

been too readily acquiesced in by us all results in needless and chronic invalidism.

Fear, too, has different aspects according to the special circumstances of a given case. It may be conscious or unconscious, but more commonly something of both. In a mining area like ours we can detect it almost invariably as a dread of being submitted to the possibility of a similar accident, and in time it may become an insurmountable revulsion which can only be controlled by prompt action, just as in an aeroplane, railway, or motor accident it is desirable for the victim to make a like journey as soon as it is practicable, if he is to be enabled to overcome his growing scruples. The law of chance enters too, and the miner is undoubtedly less well placed than most others, as he recognises very readily.

These words—shock, grievance, fear—are not medical words at all, and therefore to us have no exact meaning or method of measurement, another example of the absence of terminology causing embarrassment when we are required to discuss their significance. But since we tread thin ice in attempting to cloak them in other language it would be better, would it not, to accept them into the medical vocabulary and give to each a generous definition. This device would go some length in obviating one handicap we have in court.

**TRAUMATIC MENTAL DISORDERS.**—Litigation has hitherto been incessant, and has altered very little in essential quality since last century, or at least since the passing of the original Workmen's Compensation Act in 1897. No more now than before is medical evidence in courts of law in a satisfactory position. A medical witness frequently expresses views which are seriously at variance with medical doctrine; as Brind puts it, "Medical bona fides are assailed and rebukes by judges are regrettably frequent," and goes on to say, "Many of the reproaches result, I am convinced, from the fact that the standard textbooks on Forensic Medicine deal with medical evidence entirely from the criminal point of view, and in criminal charges the evidence required from the ordinary medical witness is usually fairly simple." But the requirements of the courts in civil cases are different and often much more complex, and with the growth of traffic accidents and claims made under the Workmen's Compensation Act, together with adjudication in pension matters, civil cases form the bulk of those in which professional evidence is required.

The influence of violence in causing mental disorders, particularly the so-called traumatic neurosis, is a very vexed question in courts of law. A single case may bring together a regular galaxy of different people supposedly to secure the ends of justice—lawyers, doctors, employers of labour, representatives of Insurance Companies, or Trades Unions acting on behalf of an injured workman, each with his own point of view and background obtruding, until the wretched workman, increasingly sensing the atmosphere, must necessarily

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muster all his resourcefulness. Many difficulties arise from the rigidity of court procedure, designed as it undoubtedly is to ensure absolute fairness. Yet is it wise to allow the claimant to be present throughout the entire hearing of his case, listening with ever-growing interest as he sees the two sides forming up, and recognising vividly who support him and who do not? Many of the more chronic phases of mental ill-health date from this embittering experience, especially if its sequel fosters a feeling of injustice. In a sensitive person this may initiate brooding, a more happy choice of word than might at first seem apparent, since it implies "sitting on" in every sense.

It is an established principle of the Workmen's Compensation Act that if a man has a natural weakness and meets with an accident which creates in him a serious loss or permanent incapacity it is of no avail for the employer to say that, if the workman had been a normal individual, the incapacity would have been trivial or transient. In spite of this principle, however, the courts have recognised that a certain mental process, namely "brooding" over an accident, may cause incapacity for work, and that the brooding is not necessarily the result of the accident. Medical opinion would hold that where brooding was so severe as to cause incapacity for work, and where any influence of the accident in causing the brooding was excluded, the brooding was undoubtedly evidence of a pre-existing neurotic or psychotic temperament. Thus medical opinion equally with the law world excludes the mental condition from connection with the accident, but it would do so on other grounds, which would not be regarded by the law as sufficient to deny compensation. Medicine would not hold a man responsible for manic-depressive insanity, but the law may regard brooding as within a man's own control. The question of brooding has played an important part in many cases where a mental abnormality has supervened after an accident, and has been discussed on several occasions in the court of appeal. It affords a good example of the different language in which lawyers and doctors speak, even though they may ultimately come to the same result.

In a given case the decision of the judge cannot be predicted, as although brooding has been recognised as a mental process which can produce definite serious results, it is sometimes regarded as due to the accident, and on other occasions was apparently thought to be under the man's own volition. The medical profession is to blame for having introduced into law cases a conception of "brooding" as a dangerous practice, but in extenuation it may be pleaded that that was many years ago and knowledge as to the ætiology of mental disorders has since been enlarged and altered. Medical opinion to-day might be more likely to hold that many of these cases were instances of manic-depressive insanity, and that the brooding was merely a familiar manifestation of that disorder. The importance still attached by the law to brooding as a mental process by itself illustrates the



tendency of medicine in the courts to lag behind scientific medicine. A statement that brooding could cause insanity would not receive much consideration at a meeting of alienists. Nevertheless the recognition by the law that a mental state, whether it be called brooding or manic-depressive insanity, may use the incidence of an accident for causing incapacity to work without being itself regarded as caused by the accident, establishes an important principle, and the application of that principle is, I submit, the correct way to handle those cases of hysteria which persist after the direct and definite effects of the accident have disappeared.

**EXAGGERATION AND MALINGERING.**—In so brief a survey as time allows it will simplify to contrast these two important aspects, although in reality they have little in common. Exaggeration creeps in both consciously and unconsciously in many cases who have become embittered during the protracted proceedings of their claim; especially those who imagine that their sufferings are not fully understood. It is a question of degree, which can best be judged by inference. A man states that he has a severe and constant headache which prevents him working or even reading, yet he is seen at a football match or at a cinema. His headache cannot be denied, only it can be established that it is less severe than he claims. A totally different matter from malingering which, in my view, is rarely found.

Psychologically the distinction between malingering and neurosis is fundamental. The neurotic symptoms are unconsciously determined and very real to the patient. The malingerer consciously and voluntarily tries to reproduce symptoms which he either previously had himself, or observed in others. He may, for purposes of gain of some kind, simulate a disease which he does not have, or unduly exaggerate and prolong minor symptoms which he has; in any case the intention is to deceive. The malingerer purposely alleges loss of function, or feigns all kinds of nervous symptoms. He complains of subjective sensations which are difficult to evaluate; for example, pains, headaches, or numbness. One of the most difficult cases I recall was a young regimental medical officer straight from the front line who announced to me that he had developed disseminated sclerosis. The history he gave was perfect, and on examination signs were not lacking—muscle weakness, with some objective sensory loss, and even an upgoing toe in one leg; but my suspicions were first aroused by the too slick story, the easily elicited abdominal reflexes, and the complete symmetry of the tendon reflexes. Under repeated questioning and examination he revealed quite suddenly his conscious purposive effort to escape a terrifying duty, as indeed it was. It seemed fair at the time to treat him as a psychopathic, and thus let him evade other unpleasant consequences. Dr T. A. Ross held the view that every malingerer is to some extent psychopathic, and in the case of the self-inflicted wound always so. With this opinion I am inclined to agree. Experienced malingerers may "throw fits," simulate paralysis, or complain of

blindness or deafness. One can recall cases of all these in soldiers, but the choice was most usually either a fit or deafness, the detection of which was never very difficult. In every case it can be shown that there is a conscious purposive effort to escape unpleasant tasks or situations, or derive actual gain through imposition. Educational background is often a measure of the ease or difficulty of detection—the intellectual type can be very clever at simulations—but one thing almost all have in common is a tendency to overdo the “stunts,” to make the exaggerations gross. Contrary to the hysteric, who likes to be repeatedly examined, the malingerer resents examination, and definitely resists all efforts at cure. When not observed the latter stops playing his rôle, so that detection is easy when the patient is off guard and not aware that he is being watched. Once the examiner's suspicions are aroused it is seldom necessary to resort to any elaborate test to determine malingering.

A malingerer has been defined by Wechsler (1935) as one who “consciously and purposely, in order to deceive, to evade responsibility, or to derive gain, feigns illness, and voluntarily tries to reproduce signs or symptoms which he really does not have, or extravagantly exaggerate minor ones which he has.” A shorter definition is that of Lord Justice Buckley, quoted by Collie, “One who is not ill and pretends that he is.”

My own view is that it is preferable to restrict the term strictly to the sense meant by the Lord Justice, and not confuse the issue by including various grades of exaggeration.

I now come to what is perhaps the most debatable ground of all—the question of assessment. What do I mean by the word “assessment”? Reverting again to the *Oxford Dictionary*, the word assessment is defined as “the action of assessment, the amount assessed.” Applying the term to its present context, we can only express an opinion after asking ourselves, has the alleged trauma been responsible for the symptoms? What disability has been produced? Is it due to organic disease or “functional” in origin? Will complete recovery occur; if not, how much? Will the man be able to return to his usual work? Then, also, our opinion might be asked about the question of light employment and its desirable nature, the expected rate of recovery, and the necessary treatment.

It is clear that the answers to these questions depend to a considerable extent upon personal judgment. In assessing the nature of many symptoms one depends a good deal on a consideration of the effect of the passage of time, and the attitude of the patient to them.

As medical men, we have to admit the responsibility for the mis-handling of many of these cases, and, as teachers, we have a serious duty to pass on the lessons from our experience to the next generation. For example:—

(1) The doctor should be trained to avoid the suggestion of serious injury, or equally of a narrow escape.

(2) Occupational therapy should be started at once and should merge into therapeutic occupation—that is, organised light work.

(3) Medical evidence must make an emphatic change from compensation to rehabilitation. The need for compensation is, to a large extent, a measure of the failure of rehabilitation.

(4) The Workmen's Compensation Acts should be revised, and probably will be very soon, so that an industrial injury should not immediately involve a potential dispute about the ownership of a sum of money. Medical issues should be decided by medical boards closely linked with rehabilitation units; and an adequate maintenance allowance should be guaranteed to the injured man as long as the medical board regarded him as disabled, and as long as he co-operated in his treatment and rehabilitation. The army system as evolved approximates to this, and on the whole has been found to work well.

(5) Such a system would mean less actual litigation but, in those instances which do reach court, it is most desirable that the claimant should not hear the evidence; also medical opinion, expert and otherwise, should be fully discussed, and so far as possible differences composed in advance. All fees should be paid out of a court pool, in order that the doctor's rôle may come to be recognised by himself and all others as being strictly that of a medical jurist, and never that of a partisan.

The point is neatly put by the late Dr Kinnear Wilson whose experience in these matters was unrivalled—"A man, famous in the Edinburgh Medical School of the middle of the last century, was Sir Robert Christison, the medical jurist, and of him Lord President Inglis, the greatest Scottish judge of the same period, said: 'The Professor went into the witness-box not in the spirit of a partisan, but in his proper office as a medical jurist, to aid the court and the jury in the elucidation of truth, and in securing the ends of justice.'"

Was this, the ideal attitude of the medical and scientific witness, adopted more generally, there would be fewer unseemly disagreements on the part of those of us who are asked to express medical opinion in Court cases.

Some of St Paul's words to the Philippians can guide us to-day: "Whatsoever things are just, whatsoever things are honest, whatsoever things are of good report, if there be any virtue, and if there be any praise, think on these things."

#### DISCUSSION

*Mr J. S. Jeffrey* advised medical witnesses in the law courts to be cautious when assessing the effects of trauma in diseases of unknown ætiology. For example, in dealing with disseminated sclerosis the judge might say: "You state that trauma was not responsible for the onset of the disease. What is the cause of the disease? And if the cause is unknown, how can the possibility of trauma be ruled out?" This point arises sometimes in Ministry of Pensions

cases, and certain diseases of unknown ætiology have to be attributed to war service for want of a better explanation.

Mr Jeffrey was interested in the question of fat embolism. He had seen cases of trauma to the limbs go on to increasing unconsciousness and death from fat embolism. He wondered if it was possible to have minor degrees of cerebral fat embolism, not strikingly evident at the time and not fatal, but causing cerebral symptoms later.

With regard to the settlement of claims, Mr Jeffrey held the view that a lump sum was preferable to weekly payments.

*Dr J. G. Sclater* agreed with Dr Slater that it was better that the claimant on certain occasions should not be present while his case was being discussed. He had recently given evidence in a case and had suggested that the claimant should be asked to leave the court, to which suggestion the judge heartily agreed.

Another point which Dr Sclater felt strongly was the opposing lawyer's attitude to the medical witness—the attempt being frequently made to suggest the doctor's incompetence to act as an expert witness. He also felt there should be a "pool payment" system whereby doctors would not be called upon as witnesses by either side, but be "neutral" and paid from this pool.

Dr Sclater held the opinion that, in cases of post-traumatic neurosis in patients whose previous psychological histories were good, the injury should be looked upon as the deciding factor with regard to the development of neurosis, in comparison with the patient whose psychological history previous to accident was poor, where the accident would appear to be only an aggravating factor.

*Colonel Cunningham* said he was glad to hear that Dr Slater stressed the value of therapeutic occupation in these cases. In the Astley Ainslie Hospital, where many such cases remained in hospital for a comparatively long time, there was no doubt that, if the patient was given something to do to interest him and take his mind off his disability, his recovery was likely to be hastened.

The attitude of the patient himself was important for, even in serious cases, if the patient was co-operative more could be done for him than for the man who was unco-operative and only interested in his own illness.

Colonel Cunningham felt that after the period in hospital, where the occupations used were selected primarily for their therapeutic value, a further stage in the rehabilitation process was required, when cases of this kind would receive work or training under controlled conditions which approached more closely to the industrial side, before they returned to their full duties.

As matters stood at present a man most frequently went straight from a hospital regime back to his own job. In certain places—Birmingham for instance—he believed that some advances towards this intermediary stage had been made, but there was nothing here of that kind at present so far as he knew.

*Dr Malcolm Smith* was of the opinion that a continued weekly pension was not a good thing—he was in favour of settlement by a lump sum.

Dr Smith felt that rehabilitation should start from the beginning of an injury, otherwise the patient tended to brood on his disability. A patient attended at S.O.P.D. on several occasions and was put into what he called a "stooky," perhaps attended the Massage Department for a bit and was eventually forgotten.

With regard to Rehabilitation Centres, Dr Smith questioned the workings of them. He had known of cases where they had very little to occupy their time—he mentioned one case who, after a short spell of daily treatment, spent his time standing in the canteen doing nothing.

*Mr J. R. Cameron* referred to the tendency to regard the giving of medical evidence as slightly disreputable. He agreed with the speaker that the undergraduate did not receive sufficient teaching in the various aspects of giving evidence in compensation cases, more stress being laid on criminal problems which are more of a rarity. Dr Slater had suggested that in self-inflicted injuries the patient was invariably psychopathic. Mr Cameron was not sure about this; he had seen many self-inflicted injuries in wartime where environment and race were apparently the main factors. He considered that rehabilitation in the type of cases referred to in Dr Slater's paper was most important. Teaching on this subject to undergraduates and post-graduates should be given an important place.

*Dr D. S. Middleton* was interested in the question of trivial injuries causing minor disfigurement. To what extent should the sex of the individual be considered in making assessment. Should the female be entitled to a different assessment or viewed only from the aspect of the injury?

*Dr Douglas Robertson* questioned the prevalency of post-traumatic neurosis. He felt that the development of neurosis due to accident in a person not previously neurotic was less common than supposed. Conditions which might previously have been considered neurotic were now found to have an organic cause; for instance, prolapsed intervertebral disc or the acro-parathesia syndrome. Other conditions might, in the future, be rescued from the scrap-heap of neurosis and found to have an organic basis.

Acro-parathesia was common in housewives during the war, and since. It is particularly common in the right arm, and may be due to carrying a heavy shopping bag. Complete rest of the arm in a sling is the only treatment necessary.

*Dr H. M. Traquair* mentioned that the late Dr T. A. Ross had strongly insisted upon a thorough and exhaustive physical examination before diagnosing neurosis. Visual impairment might follow injury. He recalled two cases of tobacco amblyopia, one in a woman who had dislocated her shoulder, another in a man who fell when running after a tram-car, who was not physically injured but nervously upset. Both subjects were heavy tobacco consumers and the injury apparently caused the disease to become manifest.

With regard to Ross's view that self-inflicted injuries were only found in psychopaths, he had not seen many eye injuries of this kind but all he had seen occurred in psychopathic subjects.

Post-traumatic impairment of vision in the healthy eye when one eye had been injured was a condition which gave much trouble to oculists especially in compensation cases. The popular idea that when one eye was injured the other must necessarily suffer from "strain" "because it had to do all the work" was completely mistaken.

Over-treatment was a fruitful cause of impairment of vision where no adequate physical reason existed. He recalled the case of a man in the 1914 War who had suffered a slight skin wound of the cheek below his left eye from a grenade explosion. The eye was bandaged and the man was sent home. Nearly a month elapsed before the bandage was removed. The eye

itself was apparently uninjured but was found to be blind. The man was paid a pension for two years and was then told that the eye must have been "amblyopic" when he entered the army. After a thorough examination and a psychotherapeutic chat the matter was cleared up by a full explanation, and in a few minutes normal vision was restored. Photophobia also was often over-treated and prolonged by the ill-advised continued use of dark glasses.

*Dr Slater*, in reply, said he understood Mr Jeffrey's hesitancy in avoiding dogmatism in such an instance as disseminated sclerosis, yet here was a case when accumulated experience alone could be convincing. Fat emboli need not be lethal, as witness a case of fractured femur dying of pneumonia in which small quantities of fat were found in and around the brain without any ante mortem sign of central nervous disturbance. It had been clearly established both here and abroad that an injured man was much more likely to resume work soon after an early lump sum in compensation than when drawing a weekly allowance.

Legal men are usually well disposed towards us, but our vacillations and reluctance to enter the witness-box have often inconvenienced and irritated them. A principle often introduced in assessment is that the award must take into account the pursuant's prospects. Colonel Cunningham's pertinent remarks require emphasis, since we err so often in a rule of thumb approach to vocational training with too scanty thought for the individual's personality, Dr Robertson knows that as methods of diagnosis advance the likelihood is that less and less will be regarded as basically functional.

The one satisfactory way in which to anticipate "brooding" is to direct the patient's mind into optimistic channels.

The president's vast experience with the many and varied eye complications of trauma shows only too clearly the numerous pitfalls open to the unwary, and especially the dangers inherent in treatment based on a faulty conception of the real cause of impairment of vision.

# URINARY INCONTINENCE FOLLOWING CHILDBIRTH, INCLUDING VESICO-VAGINAL FISTULÆ

By J. CHASSAR MOIR \*

Nuffield Professor of Obstetrics and Gynaecology, University of Oxford

## I. STRESS INCONTINENCE OF URINE

*Introduction.*—"The operative treatment for the relief of stress incontinence of urine fails in 40 per cent. of cases" (Millin, 1946). This statement by a responsible urologist serves to focus attention on the first subject I have chosen for this evening's discourse.

Naturally, the degree of success of operative treatment for stress incontinence of urine associated with cystocele depends on the type of case dealt with, the form of operation used, and the thoroughness and care of the operator. Personally, I should put the proportion of relapses very much lower than the figure mentioned. My colleague J. A. Stallworthy (1940) analysed the results of a series of colporrhaphy operations for the various indications performed by eight different operators in the Chelsea Hospital for Women. It was found that 10 per cent. of the patients continued to have "troublesome" and a further 6 per cent. "slight" incontinence of urine. But the exact proportions of failures need not concern us now; the point is that all gynaecologists who have conscientiously followed up their cases will admit that there is a small but disquieting minority in which the symptoms of stress incontinence are in no way improved, and even a few cases in which the patient declares that the control of the bladder has been made worse by the operation.

Now, I hope that these remarks will not be misunderstood. The orthodox plastic operation is safe and is usually effective. I therefore believe it should be employed in the first instance. It is to the resistant case I now wish to draw your attention—the patient on whom the operator has already, so to speak, "worked his thunder," but who remains as wet as ever.

*The "Sling" Operations.*—In recent years there has been a sudden interest in America and this country in what have been termed the "sling" operations for the correction of stress incontinence. Now, these operations are not new, and for many years procedures of this sort have been used by a few operators in various medical centres. In 1929 I watched Werner in Vienna perform the Goebel-Stoeckel operation for stress incontinence; I remember marvelling at its ingenuity, and marvelling also that such an outrageously radical procedure—for so it seemed—should be considered necessary for the cure of so simple a condition. Subsequent experience, however, has chastened me; and when Aldridge (1942) of New York described

\* A paper given to Edinburgh Obstetrical Society, 12th March 1947.

his new form of sling operation, I quickly adopted it and have used it with increasing satisfaction in the resistant case to which I have just referred. The steps of this operation are shown in Figs. 1 to 8.

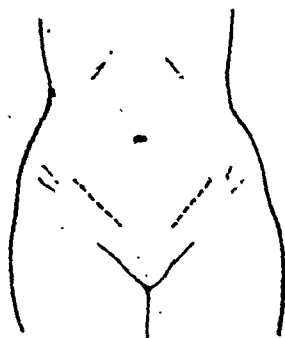


FIG. 1.—*Aldridge Operation*—  
Position of incisions.

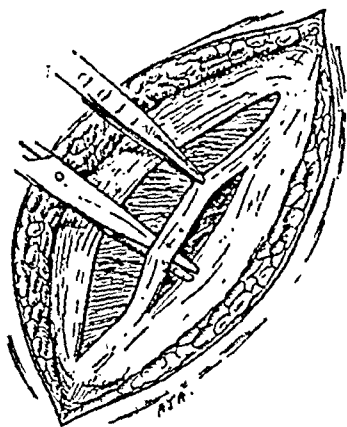


FIG. 2.—Cutting fascial strip from  
aponeurosis of muscles of ab-  
dominal wall.

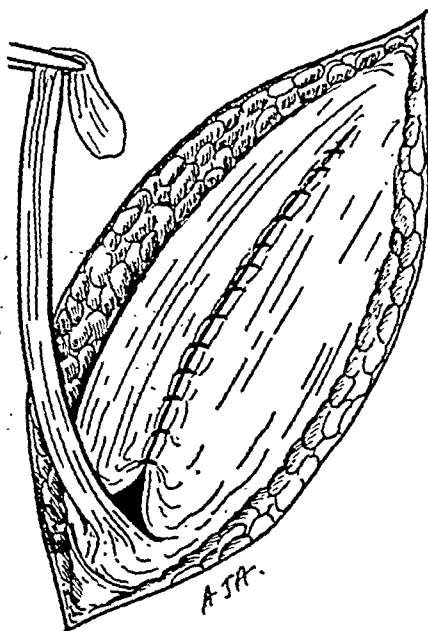


FIG. 3.—Closing fascial incision leaving fascial strip attached by its base to rectus muscle 1 inch above pubis. The opening is shown through which the strip is drawn down, through the rectus muscle and the space of Retzius, to the vaginal incision.

Soon after Aldridge's publication, Studdiford (1944) of New York proposed another modification. Instead of using a fascial strip from each side of the abdominal wall he employed one strip only, obtained by a long vertical incision. After wide separation of the recti muscles



and displacement of the bladder from behind the pubes, this strip was threaded down into a tunnel round the urethra (previously dissected out from below as in the Aldridge technique) and brought up on the

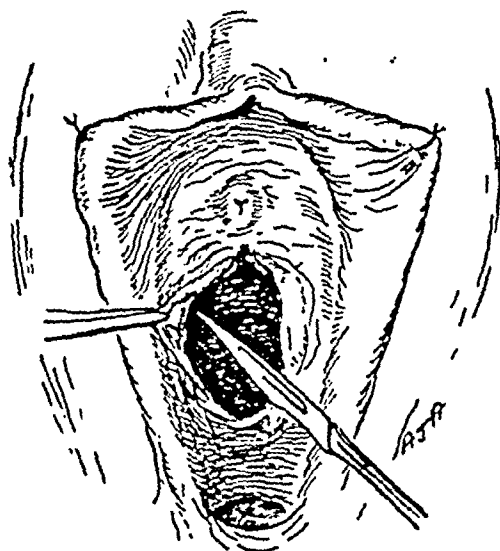


FIG. 4.—Dissecting vaginal wall from urethra to reach pubic ramus.

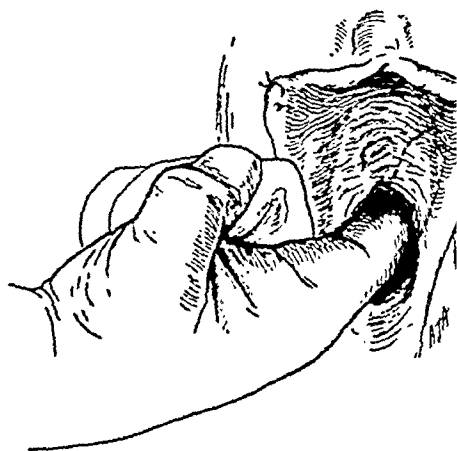


FIG. 5.—Inserting finger to feel for descending ramus pubic bone, 1 inch lateral lower margin of symphysis.

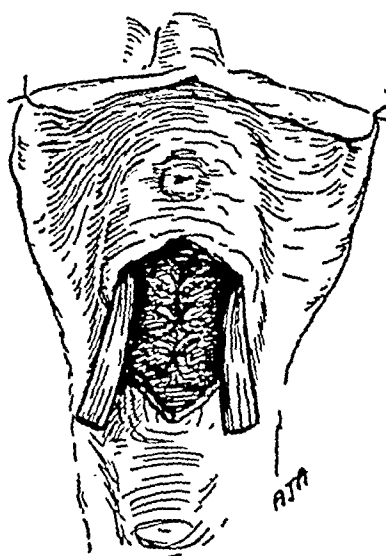


FIG. 6.—Fascial strips have been brought down, through the space of Retzius, by means of long curved forceps (uterine packing forceps).

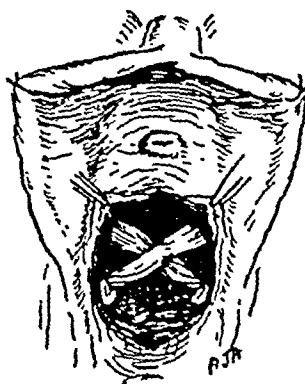


FIG. 7.—Fascial strips crossed moderately tightly under upper portion of urethra and secured by nylon sutures.

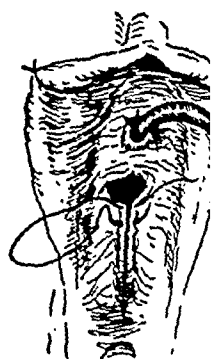


FIG. 8.—Vaginal incision closed by a "butterfly" stitch of nylon. Catheter inserted into bladder and stitched to the meatus.

other side to be attached near the lower end of the opposite rectus muscle. The "threading" manœuvre is simplified if a thin rubber tube has been previously placed in the tunnel when that was fashioned from below. To the end of this tube the free end of the fascial strip is tied, and the strip then drawn through the prepared channel by

pulling on the other end of the tube. This modification, which eliminates a difficult part of the operation, was proposed and tried by my house-surgeon, R. C. Gill, and I am interested to see that the same procedure has since been independently described by Studdiford himself.

While these forms of the "sling operation" were being tried in U.S.A. and in this country, Millin (1946) of London devised yet another form of bladder-neck support by means of fascial slings. In his method, all the dissection is done from above. Through a wide Pfannenstiel incision two transverse fascial strips are fashioned by incising the coverings of the abdominal wall muscles; each strip is freed at one end but left attached at the other, one to one side, the other to the other. A wide exposure of the space of Retzius is now made, and, with careful dissection, a passage is opened round the upper part of the urethra, taking great care to avoid penetrating either bladder or vagina. With a special instrument shaped like a rib-raspatory the fascial strips are, separately, passed down one side and up the other. Their free ends are then secured to the fascia remaining over the lower parts of the recti muscles, or, in Read's modification, to the body of the companion strip of the opposite side. A double sling or hammock is thus provided on which the urethra and bladder neck is supported.

It is clear that all three operations achieve a similar purpose. The bladder neck is drawn up, and the urethra is somewhat lengthened and compressed. When the patient coughs or otherwise contracts her abdominal muscles the sling automatically tightens on the urethra. Obviously, care must be taken not to make the sling too tight, for micturition will then be impossible; and it is the exercise of judgment on this point that is perhaps the most difficult feature of all these operations. Since all three procedures seem to give equally good end-results, a decision regarding choice of technique depends on a variety of considerations which I shall now enumerate.

Regarding the *Aldridge operation*, the following are *points in its favour*. (1) It is relatively simple. (2) No separation of the recti muscles is required. (3) The bladder is not displaced from behind the symphysis pubis. (4) The tension on the sling can be adjusted with a fair degree of precision. The following are *points in disfavour*. (1) Two different operative approaches are necessary. (2) The patient's position must be changed during the operation. (3) It is time-consuming. (4) There is a theoretical risk of sepsis ascending from the vaginal incision.

Regarding the *Studdiford operation*, the following are *points in its favour*. (1) A single vertical incision can be used instead of two lateral incisions as in the Aldridge operation. (2) The fascial strip is continuous so that no stitching or joining is required below the urethra. The following are *points in its disfavour*. It shares with the Aldridge operation the disadvantages (1), (2), (3) and (4) already cited. In

addition (5) the fascial strip is difficult to obtain without encountering a good deal of bleeding. (6) The strip contains weak portions at the tendinous intersections of the recti muscles, which may tear if much tension is applied. (7) The recti muscles are freely separated and the space of Retzius is widely opened. (8) The correct tension is more difficult to gauge than it is in the Aldridge operation.

Regarding the *Millin operation*, the following are *points in its favour*. (1) It can be performed by the abdominal approach alone. (2) It can be done in less time than is required for the other two operations. (3) Since the vagina is not opened the risk of ascending infection is eliminated. The following are *points in its disfavour*. (1) The recti muscles are freely separated and the space of Retzius is widely opened. (2) The bladder neck is liable to injury during the deep dissection that is required. (2) The vagina may be inadvertently opened. (3) The correct tension to put on the slings is difficult to gauge.

From this it will be appreciated that the selection of operation depends largely on the predilection of the individual surgeon. Personally, I think that the Aldridge operation does all that is required and does it with the minimum of risk. Although somewhat time-consuming it is, relatively speaking, a safe procedure, and—a point that particularly appeals to me—it is an operation of precision. In none of my cases of this or of the Studdiford operation has there been any sign of infection.

*Results.*—As already stated, I do not consider it justifiable to use a sling operation until the orthodox colporrhaphy has been tried and found ineffective. In consequence, the number of cases I can record is as yet small. I and my assistants, Scott Russell and G. G. Lennon, have performed the Aldridge or Studdiford operation fourteen times, and have been well pleased with the results. With one exception (to be mentioned later) the stress incontinence has been entirely cured or very greatly relieved. In the two or three cases in which there is still a slight escape of urine, that symptom appears only on sharp exertion; probably the sling was not adjusted quite tightly enough. Included in those figures are 4 cases in which there had been a vesico-vaginal fistula with destruction of the musculature of the bladder-neck; the sling operation was performed subsequent to the operative closure of the fistula.

So far as it is yet possible to determine, the results are permanent, but it must be stated that in one patient—a vesico-vaginal fistula case in which the urethra had been completely destroyed and subsequently reconstructed by operation—some incontinence returned eighteen months after the operation.

## II. THE VESICO-VAGINAL FISTULA

*Historical Note.*—In days gone by this was a deplorably common sequel to hard childbirth. Nowadays, although obstetric misadventure still exacts its toll of fistulæ—both the form brought about by tearing

consequent on difficult instrumentation, and the form brought about by pressure necrosis of the bladder-neck—those injuries are fortunately rare. True, a new form is now with us—the fistula caused by injury inflicted during a difficult gynaecological operation—but that too is a rarity; and so far as this country is concerned, individual gynaecologists see but little of this class of work. Very different are the conditions in certain other parts of the world—for example, parts of India and Africa including Egypt—where the vesico-vaginal fistulae are so common as to constitute a major surgical problem.

Listen now to the words of our own medical forebear. Sir J. Y. Simpson in this school described the vesico-vaginal fistula as “the most depressing and deplorable of all the infirmities of which woman is liable, a condition looked upon as beyond all relief and hope.”

No one can refer to the history of the vesico-vaginal fistula without mention of J. Marion Sims (Moir, 1940); and if there is in this meeting any one who has not read Sims's book, *The Story of My Life*, I can only say that one of the most fascinating tales in all medical literature lies before him. Although Sims is usually credited as the first to cure the vesico-vaginal fistula, this is not strictly true. Others, notably Gossett in London, Peter Mettauer in Virginia, and Heyward in Boston, to mention only a few, had all operated with success, and—what is more significant—had used some of the very methods to which Sims later attributed his success. Indeed, it is a little hard to believe that Sims had not, consciously or unconsciously, already absorbed some of Mettauer's ideas when he himself evolved the method of treatment that was to be so conspicuously successful. Be that as it may, it is beyond doubt that to Sims belongs the credit of breaking the conception that the vesico-vaginal fistula was a mutilation beyond surgical aid. By exemplary courage in adversity, by extreme tenacity of purpose and, not least, by remarkable operative dexterity gained through years of rigid training and discipline, Sims arrested the attention of his contemporaries and convinced them of the high promise of surgical methods. To use a modern turn of speech, he it was who put the surgical treatment of the vesico-vaginal fistula “on the map.”

*Choice of Operation.*—This excursion into history enables me to stress a point in the technique of repair which I believe is important. Most modern writers imply that the classical operation of Sims and his contemporaries has been superseded by more modern methods. Now a study of Sims's work and that of his assistant and successor Emmet, shows that these early workers succeeded in curing as great, or nearly as great, a proportion of cases as we cure to-day by modern methods, and did so without the advantages we now possess in the form of anæsthesia, infinitely better instruments, lighting equipment and operation facilities in general. I therefore suggest that, far from being outdated, the older technique still merits attention, and can to this day be used with great advantage in many cases.

Of Sims's work it is stated that relatively early in his career he cured 215 out of 261 cases of fistula (vesical and rectal); 36 more were greatly relieved, and only 9 were considered incurable. Many of the failures or partial successes were in patients who did not continue with the treatment, or who, we are told, were discharged from hospital because of drunkenness or other misdemeanour.

Unfortunately, a simple and accurate description of the methods of these masters is hard to find, and it is only by gleanings from scattered writings that one can form any clear picture of their work. Too often does this happen in medicine. An old and sound method of treatment is eclipsed by some innovation—enthusiasm for the new causes neglect of the old; and before long a generation of practitioners

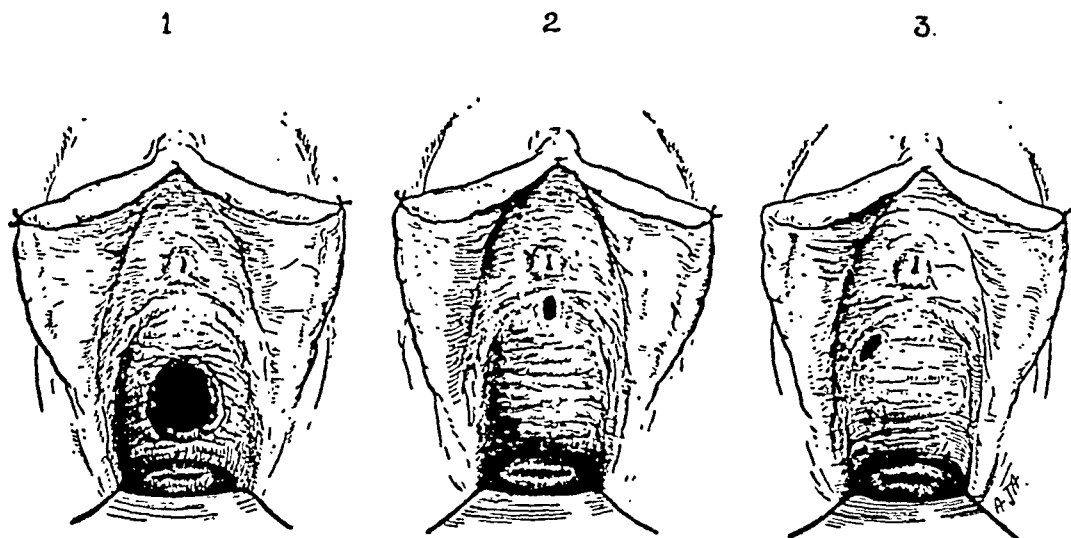


FIG. 9.—Three forms of vesico-vaginal fistula :—

- (1) Large fistula involving base of bladder. This form is not necessarily difficult of closure.
- (2) Urethro-vaginal fistula. This form may be very difficult to treat (see text).
- (3) Fistula adherent to descending ramus of pubic bone. Mobilisation of the fistula is essential before closure is possible.

appears to whom the previous methods seem unworthy of heed, or to whom they are even quite unknown.

To come now to the point. Most modern operators stress the importance of mobilising the bladder by lifting up wide vaginal flaps and then thoroughly freeing the bladder from any fibrous bands that restrain its mobility; this done, each organ is then separately sutured. An excellent account of this technique is given by the late Colonel Hayes (1945), to whose last paper I commend your attention. Benion Thomas (1945) has also made an important contribution to this subject, and, above all, Mahfouz's monograph (1938) provides a wealth of information concerning the technique of operative repair in general.

*Details of Operative Repair.*—For my own part, although I use the flap-splitting method when it seems specially indicated—as, for example, in some cases of urethral fistula or vesical fistula adherent to

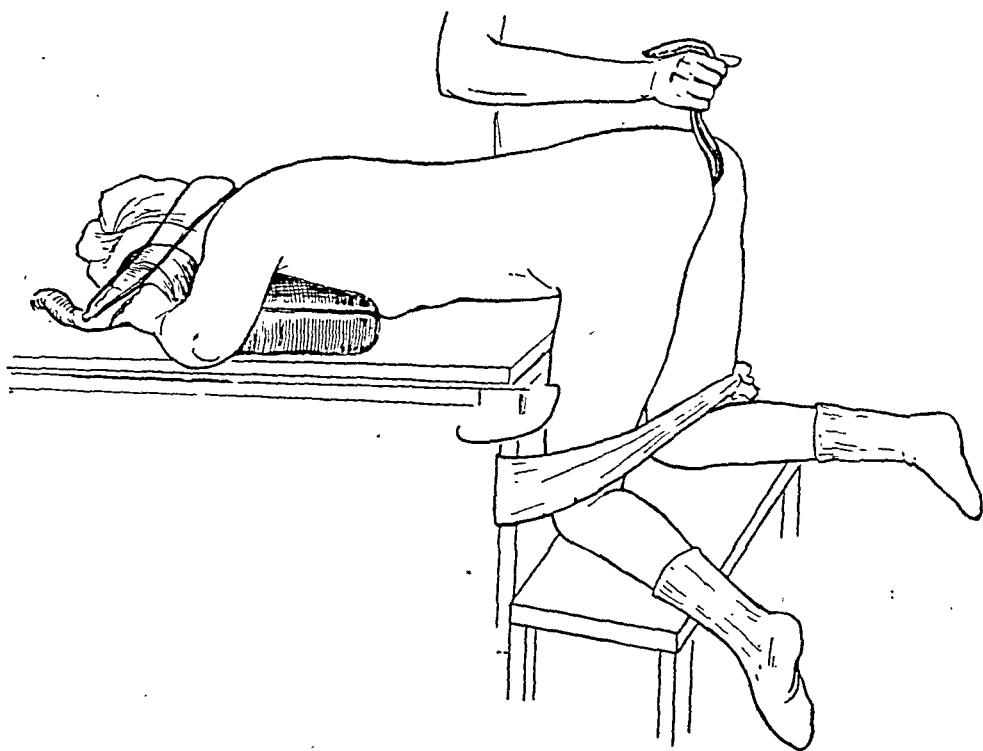


FIG. 10.—Position for operation when exposure in lithotomy position is difficult.  
*Note.*—The lower abdomen is clear of the top of the table.

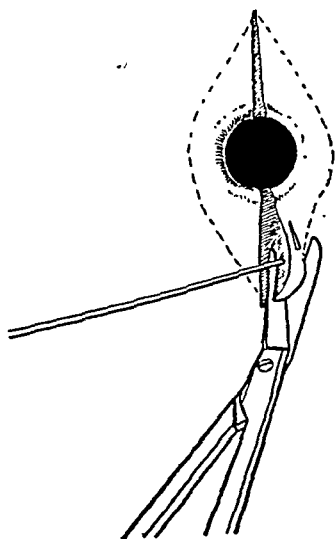


FIG. 11.—Method of incising edges down to, but not including, bladder mucosa.

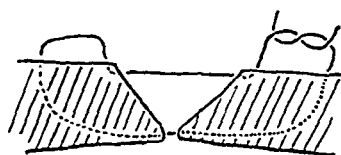
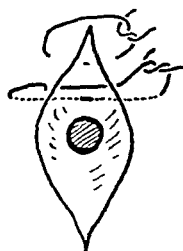


FIG. 12.—Method of placing the nylon or silver-wire sutures.  
 One "ordinary" and one mattress suture are shown.

the pubic ramus—I consider that the technique is, in the majority of cases, needlessly drastic and difficult. In general, I much prefer the simple "saucerising" operation depicted in the accompanying pictures (Figs. 9 to 15). Please note that to give this method the title of the "edge-paring operation," as is so often done, is to convey a totally inadequate idea of its form and extent.

It may be questioned whether, if free mobilisation of the bladder walls is omitted, the raw edges can be brought together without tension of a degree that would hinder or prevent their union. This is a matter of considerable importance. In some cases there is, undoubtedly, a considerable strain on the sutured area after this method

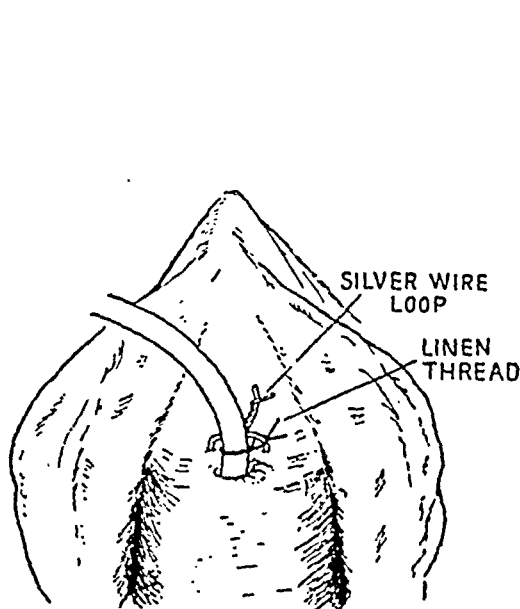


FIG. 13.—Method of securing catheter by linen thread to a silver-wire "anchor" stitch. The catheter can be removed and re-inserted without removing the "anchor."

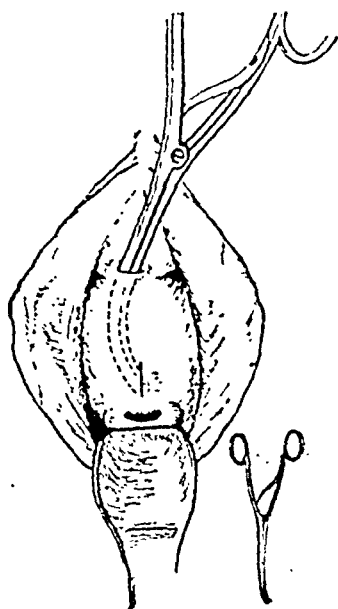


FIG. 14.—Method of making a vaginal cystotomy for temporary drainage purposes. Tracheotomy dilators are passed through the urethra and the points made to impinge on the bladder wall just below the cervix. (Position of fistula is omitted for sake of clearness.)

of repair; the tense bands or ridges that extend towards the side walls of the vagina can be easily recognised by finger palpation. But this dangerous tension can usually be overcome by the simple expedient of dividing the bands on one or both sides, making the incisions parallel to the suture-line of the repaired fistula, and as far from it as is practicable. The beneficial effect is at once evident: the new incisions gape widely, and a new laxity appears of the tissues in the region of the repaired fistula. Although the relaxation-incisions may at first bleed rather freely, this loss soon changes to a slow ooze which, as a rule, clears up completely in twenty-four hours. No suturing is needed; the wounds quickly granulate over and heal in a remarkably short time—certainly in less than three weeks.

Other important points in technique are these.

If the exposure of the fistula is difficult with the patient in the lithotomy position, I turn her over so that she kneels on a low stool at the bottom of the operating table (Fig. 10). This procedure was suggested to me by Grey Turner, and I have found it of great advantage in some difficult cases. Occasionally a free episiotomy is also required in order to gain adequate access to a high-place fistula.

The following instruments are essential. Sims's right-angled sharp hook ; a long, fine dissecting knife with No. 11 Bard Parker blade ; a long, fine dissecting forceps (three teeth in 2) with a clipping device

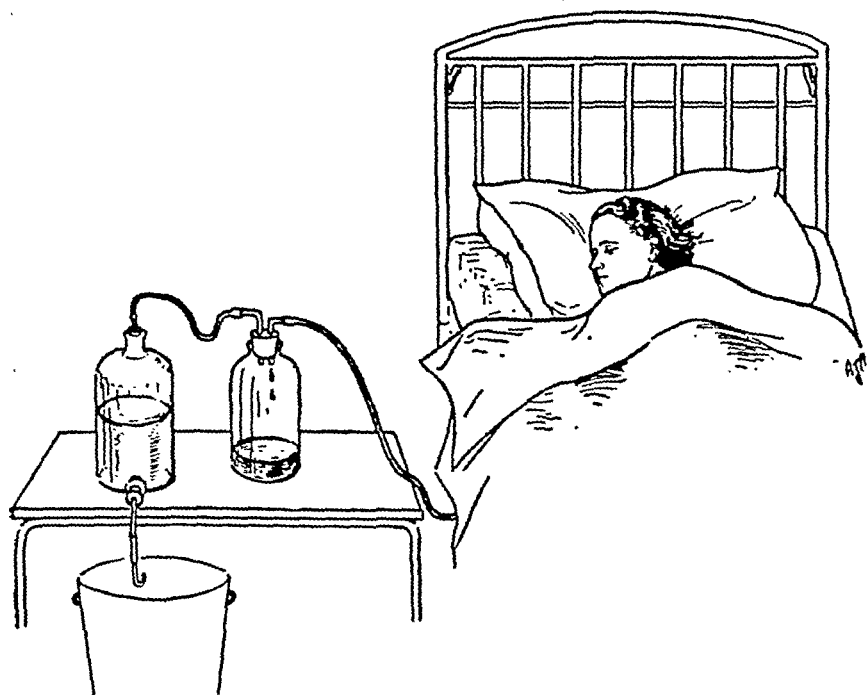


FIG. 15.—Method of suction drainage. The drip tube is narrowed and turned up at its end ; this prevents any entry of air into the suction-bottle.

on the shanks ; two long-handled scissors, one angled on the flat and one with the cutting portion bent  $90^\circ$  to the shaft. It is a great advantage to have a sucker for keeping the operation field free from blood ; this is very much better than the use of relays of small swabs.

Suture material is highly important. I am convinced that many failures in fistula repair result from a too-free use of catgut which, in tissues of low vitality and in the presence of mild sepsis (inevitable in fistula work), causes an exudation of fluid and consequent failure of union. My preference is for silver-wire of No. 19 gauge ; but nylon, No. 5 size, is also suitable, and to anyone who has not mastered the use of wire sutures, is easier of manipulation. The sutures are left in for not less than twenty days. If catgut must be employed (and on rare occasions it is necessary for the bladder or urethral edge) only two or



three interrupted sutures should be inserted, and these should be of the thinnest available gauge of chromicised gut.

After the closure of the fistula great care must be taken to syringe out the bladder thoroughly in order to remove every fragment of blood-clot. A plain catheter with extra lateral eye is then tied into the urethra (Fig. 13). (A self-retaining catheter should *not* be used, for the mushroom-head may press harmfully on the repaired fistula.) Suction drainage should be maintained for at least twelve days (Fig. 15).

When the urethra is extensively involved it is better to avoid a urethral catheter, and, instead, to drain through a separate vaginal cystotomy (Fig. 14). A stout catheter is inserted through this opening and stitched to the cervix or vaginal wall. It is removed at the end of a week, after which a thin catheter is inserted into the now healed urethra, and bladder drainage continued for a few more days. The cystotomy incision heals spontaneously within a week (Moir, 1942).

*Results.*—My experience of vesico-vaginal fistula cases is small in comparison with that of workers such as Mahfouz Pacha of Cairo, who has reported his experience with a series of more than 400. To date, my cases number only 40, but these have mostly been referred patients in whom there has been some feature of particular difficulty resulting in the failure of previous attempts at closure. Some of my patients have had numerous previous operations (10 or more) both by the vaginal and by the supra-pubic routes. One woman had extensive sloughing of the vagina after radium treatment, with combined bladder and rectal fistulæ. Three patients had a complete destruction of the urethra (Moir, 1945).

With the exception of malignant cases, and also of deliberate vaginal cystotomies (all of which have healed spontaneously), I have dealt with every vesico-vaginal fistula seen, and thus far have been fortunate in securing closure by a vaginal operation in every case. In a few instances two operations have been necessary to secure complete closure. As mentioned previously, the seemingly good result of the operation has, in a very few instances, been marred by some degree of stress incontinence of urine—the result of the extensive damage to the sphincteric area of the bladder. These patients have been cured or at least greatly improved by the Aldridge "sling" operation as mentioned in the earlier section of this paper.

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## DISCUSSION

*Dr Douglas Miller* said that stress incontinence had very little relationship to the actual degree of anterior vaginal wall prolapse, and the repair of a cystocele (or the insertion of a controlling pessary) did not improve the stress incontinence, for which special operative measures were necessary. In his experience, when such special measures were carried out during a prolapse operation, failures were approximately 5 to 10 per cent., the bulk of them being in cases who had had previous unsuccessful operations. He himself had very limited experience of the sling operation; the Aldridge operation attracted him more than the others described by Professor Moir.

In his wards three vesico-vaginal fistulæ had been seen in the last seven years. The condition was not frequent in the East of Scotland, and the opportunities for becoming proficient in its surgical treatment were therefore few. Professor Moir's paper had thus been particularly useful.

Dr Miller enquired whether Professor Moir carried out a cystoscopic examination as a pre-operative measure, and what was the dye, if any, he used to demonstrate a small fistula the location of which was difficult.

*Dr E. C. Fahmy* said that after seeing an Aldridge operation most admirably carried out by Professor Moir, he had carried it out himself on one patient, who was incontinent in spite of two attempts to cure her condition by plastic operations confined to the vagina. He had found less difficulty than he had expected and the final result had been satisfactory. He felt that the Aldridge technique had advantages, but cases had to be carefully selected.

Vesico-vaginal fistulæ were comparatively rarely seen now in Edinburgh. Dr Fahmy had handled only about 7 cases that he could recall. In two multiparæ of menopausal age he had had difficulty in mobilising the bladder; and in these cases he had carried out vaginal hysterectomy, when it was immediately possible to close the fistulæ with ease, primary healing following. In one of these cases the fistula was a vesico-vaginal one. In another case which he had been asked to see in 1946 for the first time, some six months after a difficult craniotomy, he had found that the entire bladder base and urethra had sloughed away. Mr R. L. Stewart carried out bilateral transplantation of the ureters in this case with complete success. However, five months later the patient reported saying there was something hanging down outside the vulva when she walked; examination showed complete inversion of the bladder. Dr Fahmy excised the mucous membrane of the whole of the bladder, plicated the muscle wall of the bladder with interrupted linen sutures, and then approximated in some degree the torn area of the vaginal wall. He left the sutures in position. The patient was now getting about and doing her housework, and she recently reported that some stitches had passed per vaginam—at least four months after operation.

*Dr Hector MacLennan* said that in operating for incontinence of urine it was desirable by careful interrogation to distinguish between stress incontinence and urge incontinence. It seemed probable that when a large proportion of failures followed vaginal operation it was because urge incontinence had been the main reason for the patient's symptoms. This seemed little if at all improved by operation. He would welcome Professor Moir's opinion on this subject.

*Mr David Band* said that he had been disappointed to hear no opinion

from Professor Moir on the ætiology and morbid anatomy of stress incontinence, a problem in which he had been interested from the standpoint of the urological surgeon called upon to deal with similar symptoms in cases of spinal cord injury. He showed lantern slides demonstrating the innervation of the bladder and its sphincter, the automatic emptying of the bladder in spinal cord injury and disease, and the improvement in such patients resulting from re-education in the use of the voluntary muscles controlling micturition. He also described a case in which he had adapted a gracilis muscle flap for control of the female urethra.

*Mr J. R. Cameron* said that in general surgery the use of fascial sutures in repair of hernia was somewhat fallen from favour. However convincing a fascial suture might appear at the time of operation, its survival was problematical. The technique of using a free graft of cutis vera in lieu of suture material had much to commend it, since its survival in tissue was good, it was well supplied with tissue cells generating both fibrous and elastic tissue, and the supply was unlimited. Mr Cameron showed lantern slides of histological specimens indicating the survival of such grafts and their powers of adapting themselves to the lines of strain in the tissues to which they had been transplanted. He suggested that the use of such grafts to form the sling in an Aldridge type operation should be very satisfactory.

*Dr John Sturrock* said that he had twice performed the Aldridge operation. In the first case he had apparently carried his dissection too far posteriorly and although in an avascular zone between fasciæ propriæ of bladder and vagina he had opened the bladder when attempting to pass through the fascial resistance experienced before entering the space of Retzius. From Professor Moir's description of the operation he now understood the reason. Repair of the bladder opening was successful and the ultimate result had been entirely satisfactory. In the second case he had been impressed at the time of operation by the delicacy of the fascial strips cut from the aponeurosis, but despite this the operation had been initially a success. However, after three months, stress incontinence returned. Dr Sturrock had then re-opened the vaginal incision, had succeeded in identifying the remains of the fascial slings, and had plicated them behind the urethra, the patient having been cured completely by this secondary procedure.

*The President* thanked Professor Moir for his paper. It was most gratifying that the guest lecturer for this session was himself a Fellow of the Society and an Edinburgh graduate who had held resident posts in several hospitals in the city before going farther afield to make a distinguished name for himself.

The President had had the opportunity of watching Dr Norman Miller of Ann Arbor, who was the fistula expert in the United States, and had been impressed with the detailed pre- and post-operative nursing care applied in Dr Miller's clinic. Professor Miller insisted that his good results were partly due to the patient being nursed almost in the knee-elbow position on a specially constructed frame both before and for ten days after operation. Professor Moir appeared to hold no such view, and the patients were nursed on their backs.

*Professor Moir*, in reply, said that he did favour a cystoscopy prior to operation. Methylene blue was a satisfactory dye for demonstration of small fistulæ. He had been impressed with Dr Fahmy's cases in which vaginal hysterectomy had allowed extra mobilisation of the bladder base, and would

certainly keep it in mind. Urge incontinence was often caused by a urinary infection and could be greatly improved by standard medical treatment in hospital, which should in any case be applied before undertaking any operation for incontinence. The gracilis flap operation was no longer required, any form of sling operation being preferable. The use of cutis vera grafts did not appear to him as very desirable. The grafts from the aponeurosis were certainly more convenient and seemed quite satisfactory in practice. Strips cut from redundant vaginal flaps to make a sling behind the urethra might be developed as a stage of the standard cystocele operation.

Dr Sturrock's experience served to emphasise that the Aldridge procedure was not so much a sling for the bladder neck as a sling for the upper part of the urethra. By keeping the dissection strictly para-urethral, the dangerous vascular zone might be avoided. In regard to the nursing position of fistula patients, the prone position offered undoubted advantages by minimising the pressure on the suture line during coughing. However, the full prone position was difficult to maintain and Professor Moir favoured a three-quarters prone position. The maintaining of a special position during convalescence was necessary in only a small proportion of cases.

# THE EVOLUTION, FUNCTION AND SCOPE OF THE MEDICAL SOCIETY \*

By EDWIN BRAMWELL, M.D., LL.D., F.R.C.P.Ed., and Lond.  
Professor of Clinical Medicine (retired)

## DISCUSSION

(Continued from p. 139)

*Mr Graham* expressed great appreciation of Professor Bramwell's paper. He said it was very stimulating to think that Professor Bramwell, who had done so much in the past for the Society, still had its interests at heart. He stressed the importance of the present and future status of the Society.

Mr Graham was of the opinion that it was necessary to consider the position of the Society and whether anything was needed to make it more interesting and, if so, what should be done. The Council, he believed, had given the matter some consideration. Professor Bramwell's suggestion that the scope of the Society should be broadened appealed to Mr Graham. Professor Bramwell had quoted a remark of Osler's regarding the importance in a medical society of clinical meetings. In Mr Graham's earlier days cases were regularly shown at the monthly meetings. The proceedings were always initiated by the demonstrations and discussion of interesting cases, and specimens were sometimes also shown. It was, however, a matter of great inconvenience to show patients at that time of night and he was sure the patients did not like it either. The ordinary clinical meetings in the past were very successful. He believed that the poor response on recent occasions was due to the fact that everyone was feeling the effect of the strenuous war years.

He supported Professor Bramwell's suggestion that there should be separate sections for Medicine and Surgery.

Many new specialities are being developed in Surgery. The clinical staffs are being increased and there should be ample material for papers at monthly meetings.

He would like to see the younger men encouraged to come forward with communications which might with advantage often be limited in extent. Short papers would be welcomed as well as the longer ones.

Mr Graham thought it would be greatly to the advantage of the Society to be associated with the Clinical Club, and he believed, too, that it would be to the advantage of the general practitioners to be able to attend any of the meetings of the Society which appealed to them.

He thought an expansion of the activities of the Society would be much to our advantage in Edinburgh. If a modest beginning were made he believed there was a good chance of developing a really useful Society for all those interested in the various branches of Medicine and Surgery.

*Dr R. A. Fleming*, who referred to the fact that he was one of the oldest living presidents of the Society, expressed his wish to second the motion and to make one or two remarks.

\* Read at a meeting of the Edinburgh Medico-Chirurgical Society on 6th November 1946.

When he was president of the Society, the bulk of those who attended with great regularity were the general practitioners. The Society did not meet their demands for medical and surgical cases and so the Clinical Club was started. When this happened it was felt that the Clinical Club would take away part of the audience and the interest of their meetings. Dr Fleming strongly urged the necessity, whether they divided into sections or not, to endeavour to get clinical meetings started again. They were not very successful latterly and it was difficult to bring patients out at this late hour. Clinical meetings were more satisfactorily carried out in hospitals. The Longmore, for example, he was sure could provide many interesting cases.

With regard to the possibility of combining specialism in its various forms with Medicine and Surgery, the two great branches of the profession, Dr Fleming felt it would be difficult. The general practitioner is very interested to hear of some specialist subject from a man who has specialised in the subject. Dr Fleming felt it would be a pity to divide up the Society into too many special parts. He had been looking through a syllabus of the London Royal Society of Medicine where meetings were held almost every day in the week and at all hours. Unless the day came when physicians and surgeons had limited hours of duty, it was impossible to attend them all.

Dr Fleming was in favour of publication of the papers in a journal of their own, as he felt it was necessary to digest the papers soon after they were read, and not to have to wait, as was the case just now.

He also urged that Professor Bramwell's paper should be carefully studied before any decision as to the future plans was taken.

*Sir Henry Wade* said that when the medical history of our time came to be written, the name of Edwin Bramwell would stand out as the Andrew Duncan of our period; but with it all he doubted if there were a dozen in the hall to-night who knew all that Professor Bramwell had done for Edinburgh medicine, as it had been carried out so quietly, unobtrusively and in the spirit of self-effacement.

Early in his career Professor Bramwell was responsible for the complete re-organisation of post-graduate work and teaching and founded the Post-Graduate School in Edinburgh, which was world-famous, and out of it grew the British Post-Graduate School of London. In doing so he had as his motto a dictum of Wilfred Trotter, that in post-graduate work the man does not come to the School but goes to the man, a factor which undoubtedly had contributed largely to the success of the Post-Graduate School of Edinburgh.

Later Professor Bramwell initiated and carried through an important scheme of statistical research, and more recently through his organising of the Honyman-Gillespie Course of Lectures and their publication in book form, he had done much to recreate the Edinburgh Hospital Reports, the restoration of which he so keenly advocated for so many years.

Sir Henry referred to the workings of the London Royal Society of Medicine. As one who had been a president of one of the sections he was in a position to discuss sectionisation. Each section of the Royal Society of Medicine is completely independent of each other. They have separate meetings or they meet another section and discuss subjects of common interest. They also had separate Annual Dinners. It was necessary, of course, that this Society should have suitable premises and facilities.

*Professor Johnstone* said that although he had been a member of this

Society for many years, he had not attended the meetings very often and did not feel he had the right to say much about the proposed alterations.

As they all knew, the Obstetrical Society was almost as old as this one, being "born in 1840 and still going strong." It could not be expected to be absorbed by the Medico-Chirurgical Society but might be willing to join a new society as a special section. He was not in a position to speak authoritatively as the question had not been discussed.

Professor Johnstone referred to a club which had not been mentioned—the Pathological Club. Professor Bramwell had made reference to pathology and Professor Johnstone was of the opinion that the Pathological Club should also be asked to join.

With regard to the *Transactions*, Professor Johnstone doubted very much whether Edinburgh could produce simultaneously a good *Edinburgh Medical Journal* and an Annual Volume of the *Transactions*. He was in favour of continuing as at present in this matter. He thought it would be to the Society's advantage to do so.

Finally, Professor Johnstone wished to associate himself with the previous speakers with regard to Professor Bramwell. He was sorry he could not be present, but it was gratifying to know that he still had their interests at heart.

*Professor McNeil* expressed appreciation and gratitude to Professor Bramwell for his interesting paper. It gave the impression that the Edinburgh Medico-Chirurgical Society was in a state of decline although this might only be temporary.

In Professor Bramwell's comparison of this Society with other societies there was a striking difference. For instance, the Royal Society of Medicine and other older medical societies of London all had premises of their own and a library—this Society had neither. When Professor McNeil first attended this Society the meetings were held in the Society of Arts Hall in George Street and then in a hall in Shandwick Place. Now it enjoyed the hospitality of the B.M.A. Professor McNeil was of the opinion that one of the first essentials to make the future of this Society secure was to acquire suitable premises, and either with a library of its own or easy access to one.

He did not think it would be practicable for Edinburgh to have a society with many sub-sections. There was still a place for a society which covered the whole field of medicine. There was much common ground between physicians and surgeons, and it was still possible to bring together in profitable discussion not only general practitioners but also specialist physicians, surgeons and obstetricians.

Professor McNeil referred to the Medical Institution of Liverpool. It had started as a library and was now a great medical institution where physicians, surgeons, general practitioners and all sections of the profession met for meetings and discussion.

*Dr Cormack* said that as he was a rather junior member of this Society, he rose with some diffidence. Like many others there, he had been a member of the Clinical Club for many years and was surprised at the suggestion that the Clinical Club was a rival of this Society. It had never struck him that such was the case. The Clinical Club was an entirely different type of society. The main attraction was its informality—discussions were informal and the social side was prominent—coffee was served. Another point—of some importance to many—was the difference in subscription. In

the Clinical Club it was only 5s. as opposed to £2, 2s. in the Medico-Chirurgical Society. If they amalgamated what was to happen with regard to this?

*Dr Fergus Hewat* expressed his appreciation of the paper and the manner in which it had been read. He could endorse Sir Henry Wade's remarks on the good done by Professor Bramwell for the Medical School of Edinburgh. Dr Hewat had worked under him in different capacities—finally as his assistant physician in the Royal Infirmary.

Professor Bramwell had raised the question, in this period of rejuvenation, of the future of the Society. It was now necessary to decide whether it was to go ahead or not. Dr Hewat felt that it was the work of the younger men to continue and was sure that they could look with confidence to their doing so.

*Dr Douglas Robertson* endorsed Dr Cormack's remarks regarding the Clinical Club and its informal tone. Their last meeting had been crowded and there had been a stimulating and helpful discussion on the subject of modern drugs in medicine. It was essentially a club for general practitioners but consultants and specialists were welcomed. One felt in the Clinical Club that the general practitioner could speak with freedom, which was one reason for its success. Dr Robertson was, however, in general agreement with the proposals put forward by Professor Bramwell. Although he had been practising in Edinburgh for twelve years and knew many consultants and general practitioners by repute and by professional contact, he knew few as friends. He felt there was room for more social activity in the medical life of Edinburgh. He suggested a club where they could meet and talk, have a meal together and play bridge if they wished.

*Mr Dott* expressed admiration for Professor Bramwell's paper so ably presented by Dr Slater. In view of Professor Bramwell's acknowledged wisdom, it was with some diffidence that he commented on the suggestions put forward but he feared the forces of disintegration. Specialists were confined in their various narrow fields during most of their working hours, and when they attended the Medico-Chirurgical meetings they hoped for admission to a broader field of medicine. Would it be possible to arrange that principal meetings of this Society should be continued on a broad basis embracing medicine as a whole, as they have done in the past, but at the same time to construct beneath this an organisation of sub-sections in various more specialised fields of interest? He did not think that a division into medicine and surgery would be profitable, as such a division is not narrow enough to give the advantage of specialised discussion, while at the same time it has the disadvantage of failing to take cognisance of all aspects of disease states.

*Dr Sinclair* was inclined to agree with Professor McNeil and Mr Dott that the Society should be very careful not to introduce anything in the nature of cleavage in the Society. He suggested that it might be possible to assemble all the information gathered from to-night's meeting so that they might formulate ideas for the Society's future.

*Dr Wilkie Millar* expressed his thanks to the Society for appointing him a Vice-President. He appreciated it particularly as he was following in the footsteps of Dr Langwill who died during last session and whom he had known since he was a very small boy.

Dr Millar had hoped the President of the Clinical Club would be present but Dr Robertson, a past president, had spoken. Dr Millar, too, had been



a president and had always taken a great interest in the Club. Members had expressed their view to him that the Medico-Chirurgical Society meetings, while they were very interesting, seldom came down to the practical level of the general practitioner requiring to be encouraged in his duties. Consequently the Clinical Club was first started under the ægis of the B.M.A. There was no reason, however, why it should not come under the wing of this Society. The point as regards the low subscription which was brought up was, however, important. It was a consideration to the young general practitioner.

With regard to the remarks about the meeting place, Dr Millar said that the B.M.A. owned two houses here. The leases were now up, and it was the intention of the Scottish Committee to review the whole position with the likelihood of extending the premises. They had been promised a considerable sum of money from the Association to carry out the extensions. When this was accomplished there should be suitable meeting places for this and other societies. He agreed that the present hall was not comfortable. Of course, it was necessary to remember that these alterations would take time. Investigations were, however, in progress.

Another essential, Dr Millar considered, was a library, or at least access to one. There was no reason why they should not start one in a small way.

Dr Millar was of the opinion too that one of the reasons of the Clinical Club's success was its social atmosphere. They met as men, not merely as members of a profession.

With regard to the publication of the papers—much could be said on both sides—the continuance of publication in the *Edinburgh Medical Journal* and reversion to the annual publication of the Society's *Transactions*, Dr Millar asked if it would be possible to suggest a middle course. The advantage of publication in the *Edinburgh Medical Journal* was that the reports of the meetings were received at a comparatively early date, whereas an Annual Volume would not provide that. Would it not be possible to publish them at short intervals—say, quarterly?

Regarding the clinical meetings, he did not think it necessary to worry unduly over their recent failure. They would naturally improve as the medical profession became less harassed as conditions got back to normal.

*Mr G. L. Alexander* expressed an appreciation of hearing such a philosophical essay to introduce this important topic. He was rather uneasy about the proposition to divide the Society into medical and surgical sections, which would tend to destroy the general character of the meetings. He feared that general practitioners in particular might in the future have a just criticism that the communications and discussions were becoming too scientific and erudite. The Royal Society of Medicine was, he considered, hardly comparable, with its large membership and in view of the number of specialists in the London area alone. He put forward a suggestion that medical and surgical clinical meetings might be held independently, though such a course would impair the general educative value of clinical meetings embracing all types of case.

*Mr Band* considered it essential for the Society to have a suitable auditorium, with tiered seats, proper facilities for showing slides, etc.; also a library or access to a library. He was of the opinion that the social side required developing, and that the Society should have a habitation.

*Mr Jeffrey* was of the opinion that the Society should divide into sections, but felt that the success of the scheme would depend on whether or not the Clinical Club came in with them. If there were only Surgical, Medical, and Obstetrical Sections the general practitioner might be lost—which would be deplorable. The Clinical Club may ask what they are to gain by joining a larger body. It was a very excellent Club, with a reasonable subscription. *Mr Jeffrey* urged the necessity for greater informality at the meetings—frank and even angry discussion, emulating the Pathological Club.

With regard to the *Transactions*, *Mr Jeffrey* felt that if there were separate sections of the Society there would be sufficient material to justify separate publication, which must be at frequent intervals. He envisaged something unpretentious like the *Transactions of the Mayo Clinic*. If publication was to continue in the *Edinburgh Medical Journal*, then the *Transactions* of the Society should be in a separate designated section and not scattered through the Journal as at present.

*Mr Ross* felt that if the Society split up it would lose its sense of proportion. Since his return from abroad he had attended several meetings and had been struck by the benefit of having discussion on a subject from both medical and surgical sides. He believed that if the Society divided, then discussions would be confined to the one side only—medical or surgical—and this benefit lost.

*Professor Murray Lyon* was of the opinion that the fact that the question of this Society's future had been brought up for discussion was proof that changes were necessary. He had seen things to criticise and had come there to-night specially to criticise. The Chairman had invited frank discussion.

One suggestion he could put forward was that the meetings were too formal—perhaps they were too highbrow. He thought that each speaker should write his paper and then memorise it or deliver it from headings. This made a lecture much more attractive. *Professor Murray Lyon* felt that in discussion too much time was taken up with back-patting. This was quite unnecessary.

*Professor Bramwell's* suggestion of a division was important, and was not, as some seemed to think, with the intention of breaking the Society up but rather to bring the Society together.

As regards the question of finance, he did not consider the subscription too much as it included the *Edinburgh Medical Journal*.

Referring to the *Transactions*, *Professor Murray Lyon* said it would be quite impossible to publish them separately. Edinburgh could not run two medical journals. At the present time in particular it was impossible to contemplate either a new publication or any return of an old one.

*Mr Anderson* was in favour of dividing into sections. He thought that most would welcome the opportunity of a greater choice of meetings to attend. He had personally always learned something at the meetings—not necessarily from the paper but from the discussions.

*Dr Fahmy* said that the trend of development in obstetric practice was for more and more of the abnormal cases to be sent into institutions for treatment. The result of this development was that obstetric work, as a whole, was becoming perhaps of less interest to the general practitioner than it was. Much of the material discussed at the Obstetrical Society meetings was of special interest only to those who followed keenly the more technical aspects of the subject, and consequently the overworked practitioner seldom turned up to the monthly discussions. In earlier years physicians, surgeons

and practitioners attended frequently, but this was the exception rather than the rule in the years immediately preceding the onset of war. There appeared to be very definite grounds for considering the advisability of the Obstetrical Society amalgamating with the Medico-Chirurgical Society under perhaps an entirely different name.

*Dr Haultain* thought that some of the speakers seemed to think that Professor Bramwell intended to put them into watertight compartments. As he understood it, that was not the intention. He imagined that at the surgical section the physicians would be welcomed at the meetings, and the same applied to the surgeons in connection with the medical section. There would be a general section where matters of interest to general practitioners would be discussed—perhaps less highbrow meetings than the others but of importance to the general practitioners. There would be obstetrical meetings where physicians, surgeons and general practitioners would be welcomed. Instead of one meeting there would be four. With regard to clinical meetings, Dr Haultain wondered if it would not be possible to hold these on Sunday afternoons.

*Dr Gillies* expressed his wholehearted support of Professor Bramwell's plan. As an officer of a section of the Royal Society of Medicine, he was in favour of sectionisation. Each branch should have its own discussions, but should meet other sections too. He referred to meetings of anæsthetists where they met other branches—for example, the surgeons. Progress could only be attained along the lines suggested by Professor Bramwell.

*Dr Traquair* endorsed Dr Hewat's and Professor Murray Lyon's remarks that it was not disintegration but integration which Professor Bramwell was trying to stimulate. As the hour was late, Dr Traquair did not intend to put forward his own views, but he saw no reason why the Society should not divide into sections.

#### *Professor Bramwell's Written Reply*

My thanks are due for the opportunity afforded me to read the contributions of the speakers who took part in the discussion, for the kind and appreciative reception given to my paper, and for permission, should I so desire, to make some concluding observations in reply.

The discussion has served its purpose. There would appear to be very general agreement that the status of the Society and its sphere of usefulness are not nowadays all they might be, while the assertion that this is a consequence of the progressive extension of the field of Medicine and the developments of specialism has not been challenged. What can we do to adapt our procedure to present-day conditions? This has been my thesis.

Our Society, which represents the activities of a Medical Centre with a world-wide reputation, should, it has been submitted, fulfil two vital functions: (a) It should prove attractive by meeting to best advantage the educative needs of *both* the general practitioner and the specialist, while (b) it should provide—a no less important function—an outlet which encourages the presentation of original communications and their publication in *Transactions* which will bring credit to the Society and the School. The alterations in our arrangements which I have suggested have been advanced with these two *essential* functions in view.

I have advocated two major proposals: (1) That in place of our present

monthly meetings we establish a medical and a surgical section, each of which should meet once a month on different days, and (2) that we invite the Obstetrical Society and the Clinical Club to join us as additional sections. I have further suggested that, when subjects of common interest arise, two or more sections would combine and that every member of the Society may, if he wishes, attend any or all of the four meetings held each month.

Mr Graham is of opinion that there should be ample material for monthly meetings of a surgical section, and this I am sure applies to Medicine. He has also stressed the encouragement the younger men would derive from the suggested arrangements. Dr Hewat too has referred to the part to be played by the younger men. This encouragement should indeed be a most important function of the Society. So long ago as 1900, ten members of our Society—all were then clinical tutors or junior university assistants and six were subsequently appointed to University Chairs—dissatisfied with the opportunities our Society afforded, established the Galenian Society. The membership of that Society, which met regularly for a number of years, was increased to sixteen, and I have no hesitation in saying that the communications its members were then capable of producing would have been eminently suitable for the suggested medical and surgical sections of this Society and for publication in our *Transactions*. I am in complete agreement with the opinions expressed by Dr Fleming, Professor McNeil and Dr Sinclair that we should proceed slowly and that it would be inadvisable to divide up the Society into too many sections. Sir Henry Wade, whom I would especially thank for his very kind personal remarks, Professor McNeil, Mr Band and others have spoken of the desirability of acquiring adequate premises of our own with a library or access to a library. This, I agree, would in itself not only stimulate the rejuvenation of the Society but would reinforce its standing as a vital factor in the activities of the Edinburgh School. We are, however, faced with the problem of finance, but we cannot mark time until this ideal is attained. Professor Johnstone, Dr Fahmy and Dr Haultain have all spoken sympathetically of the establishment of sections, and the two first-named speakers have expressed their personal opinions to the effect that the Obstetrical Society might consider joining as a section a *new* Society. This raises the question whether our Society might not change its designation to the Edinburgh Society of Medicine, or some such title, a suggestion which is, I think, deserving of most serious consideration. Mr Dott and Mr Alexander have expressed doubts as to the advisability of forming medical and surgical sections. But the surgeon, as Dr Haultain has said, would doubtless be welcomed at meetings of the medical section, and *vice versa*. I do not propose, however, to return to this question which I have discussed in my paper. As the President, Professor Murray Lyon and others have pointed out, my aim has been to integrate, I might say to preserve and further integration, and at the same time to make the Society more attractive and to stimulate the output of communications. Dr Wilkie Millar, an original member and a former president of the Clinical Club, sees no reason why the Club should not come under the wing of the Society, and he, Dr Cormack and Dr Douglas Robertson, another former president, have spoken of the informality of its meetings. But I see no reason why the Club should not retain its informality if it becomes a section of the Society. Those who are not already members of this Society would, if they joined, as Mr Anderson and others have pointed out, be able to attend any or all of the four monthly meetings. Some of the communications presented

to this section might, with the approval of the section, form a special feature and add materially to the value of the *Transactions*. I sincerely hope with Mr Jeffrey that the Clinical Club will decide to co-operate, for the proposed scheme, which would I believe be a real advance in progress, will be defective if we do not include a section adapted to meet the practical demands of the general practitioner. All will agree with Mr Ross who spoke of the value of discussions from both the medical and surgical points of view. This would be met by combined meetings of two or more sections as occasion arises. Dr Gillies has welcomed the proposed sectional arrangements. At some future date it may be considered desirable to form a section for anæsthetics, but until that time comes the surgical section would no doubt arrange to meet the wants of the anæsthetics. Professor Murray Lyon's suggestion that communications might with advantage be spoken rather than read will, I am sure, be generally approved. I realise, as he says, that it might be very difficult at present to run two medical publications in Edinburgh because of the paper shortage. This bottle-neck can, however, only be temporary, and I am firmly of opinion, speaking as one who has had some years of experience in the sub-editing of a monthly journal, that, with the increase of material the suggested new arrangements will I believe provide, Edinburgh should be able to produce two separate very successful medical publications—the *Edinburgh Medical Journal* and our *Transactions*—well worthy of our reputation. If the *Transactions* are published separately they might with advantage, as our Editor, Mr Jeffrey, has suggested, come out at intervals, perhaps quarterly.

This discussion, in which so many speakers have taken part, should I think prove of real service in enabling the Council to decide whether changes in our policy are called for and, if so, to present recommendations which in their opinion would prove of general benefit and reinforce the virility, status and prosperity of the Society.

## NOTES

A QUARTERLY Meeting of the College was held on Tuesday, 15th July, the President, Dr D. M. Lyon, in the Chair. Drs Joseph Bryant (Carlisle, Lanarkshire), Thomas Elliot Elliot (Leicester), James Dunsinor Allan (Bothwell, Lanarkshire), Thomas Ferguson Rodger (Glasgow) and Robert William Craig, O.B.E. (Edinburgh) were introduced and took their seats as Fellows of the College. Drs John Craig (Aberdeen), John McGhie Rogan (Glasgow), James Macmaster Macfie (Edinburgh), John Craig Rose Greig (Kirkcaldy), Alistair William Wright (Edinburgh), Neil Macmichael (Edinburgh), Charles Cameron (Edinburgh) and James Alan Longmore Gilbert (Edinburgh) were elected Fellows of the College. Drs Richard White Bernard Ellis (Edinburgh), Simon Btsh (Tel Aviv, Palestine), John Paul Jones Paton (Thornhill, Dumfriesshire), Vernon Hindmarch Wilson (London), Alfred John Tinker (Johannesburg), Leon Ferdinand Earl Lewis (Trinidad), Philip Lawrence Eric Wood (London), Justin Hilary Goonewardene (Colombo, Ceylon), Solomon Joel Fleishman (Johannesburg), Arthur Alun Williams (Middlesbrough, Yorks), Alfred William Blair Edmunds (Edinburgh), Lawrence Garvie Woods (East London, S. Africa), Joseph Charles Williams (Pretoria, S. Africa), Alexander Alan Guild (Airdrie, Lanarkshire), Neil Robertson Stewart, Jr. (British Columbia, Canada), David Cameron Haig (Edinburgh), Ronald Foote Robertson (Perth), and Stephen Henry Brunton Blaikie (London) were elected Members of the College.

At a Graduation Ceremonial held in the McEwan Hall on Wednesday, 16th July 1947, the following degrees were conferred :—  
**University of Edinburgh.** *The Degree of Doctor of Medicine* :—Louise Frances Winifred Eickhoff, England, M.B., CH.B., 1937; Richard Oliver Gillhespy, England, M.B., CH.B., 1937 (*In absentia*); Leslie Stuart Glass, Scotland, M.B., CH.B., 1940 (*In absentia*); Matthew Hunter, England, M.B., CH.B., 1935 (*In absentia*); Maxwell Shaw Jones, South Africa, M.B., CH.B., 1931 (*Awarded Medal for Thesis*); James Mitchell Kerr, Scotland, M.B., CH.B., 1934 (*In absentia*); Hugh Mackenzie King, Scotland, M.B., CH.B., 1928 (*Commended for Thesis*); Samuel Lipetz, Scotland, M.B., CH.B., 1922; Richard Maurice Sotherton McConaghey, England, M.B., CH.B., 1931 (*In absentia*); Douglas Brock Peterkin, Scotland, M.B., CH.B., 1937 (*Commended for Thesis*); James Alexander Ross, M.B.E., Scotland, M.B., CH.B., 1934 (*Commended for Thesis*); John Norrie Swanson, Scotland, M.B., CH.B., 1942; Godfrey Beckwith Tait, Scotland, M.B., CH.B., 1939; Edward Robert Charles Walker, B.A.(CANTAB.), Scotland, M.B., CH.B., 1923 (*In absentia*); Alastair William Wright, Scotland, M.B., CH.B., 1936 (*Highly Commended for Thesis*).

*The Degree of Doctor of Philosophy* :—Oscar Olbrich, M.D. (VIENNA), F.R.C.P.E.

*The Degrees of Bachelor of Medicine and Bachelor of Surgery* :—Margaret Yool Abbey, Scotland; Robert MacGregor Aitken, Scotland; William Stanley Alastair Allan, England; Beatrice Margaret Allen, England; Marjorie Rae Allison, Scotland; Dick Wardrop Anderson, England; Ernest Armitage, Scotland; Henry Satorius Bannerman, Gold Coast; Thomas

Laird Barclay, England ; Matthew Anum Barnor, Gold Coast ; Mary Stewart Somerville Barr, Scotland ; Doris May Beaton, Scotland ; Kenneth William Blaikie, Scotland ; Iris Margaret Lemprière Bowman, England ; Robert Alexander Bremner, Scotland ; Margaret Sheila Brooks, Scotland ; Elizabeth Loudon Brown, Scotland ; Ian Fraser Bruce, Scotland ; James Glen Stewart Buchanan, Scotland ; Anne Marjory Calder, Scotland ; Duncan Murray Cameron, Scotland ; James Campbell, Scotland ; Mary Gray Smith Campbell, Scotland ; Sheila Helen Cattnach, Scotland ; Roma Catherine Cessford, Scotland ; Margaret Menzies Chalmers, Scotland ; James Alexander Lamb Clark, Scotland ; Marianna Irene Hanka Clark (*née* Goldmann), England ; Bernard Harold Colman, England ; Janette Galloway Cowie, Scotland ; Henry Park Croasdale, England ; Joseph Porter Crowdy, England ; Jean Mary Dance, England ; Margaret Sheila Dawe, England ; Derek William Dawson, England ; John George Dickson, Scotland ; Thomas Campbell Dow, England ; Hugh Arnold Freeman Dudley, Eire ; Stella Paterson Eadie, B.Sc., England ; Patrick Norman Edmunds, Scotland ; Emmanuel Evans-Anfom, Gold Coast ; Peggy Everett, England ; Doreen Innes Falcy, Scotland ; Robert Somerled Cameron Fergusson, Scotland ; John Findlater, England ; Thomas Scott Forsyth, England ; Marion Gardiner Foster, Scotland ; Thomas Galla, Hungary ; John Martin Hagen, Scotland ; Eileen Vanora Haldane (*née* McWilliam), B.Sc., Scotland (with Honours) ; Frank Halliday, Scotland ; Donald MacArthur Hancock, Wales ; Emma Paton Harrison, Scotland ; Dinah Constance Milne Henderson, Scotland ; Elizabeth Hill Law Henderson, Scotland ; Irene May Henry, Scotland ; Patricia Mary Hollis, England ; Anthony Hordern, England ; Evan Osmond Leyshon Hoskins, Wales ; Margaret Jean Isobel Howat, Scotland ; Mary Howson, England ; James Hughes, Scotland ; Douglas Gilbert Hutchings, Wales ; Maurice Hyman, Scotland ; Colin William Gardner Irvine, Scotland ; John Alexander James, Scotland ; Isobel Alice Duke Jarvis, Scotland ; Robert Douglas Johnstone, Scotland ; Donald Keith, Scotland ; George Stewart Kilpatrick, Scotland ; Arthur Henderson Kitchin, Scotland ; Dorothy Irene Klein, England ; Margaret Joyce Kyle, Scotland ; Grace Jeffrey Lang, Scotland ; Patrick Millar Littlejohn, Scotland ; John Duncan Ott Loudon, Scotland ; Robert Guthrie Loudon, Scotland ; Clifford Cuthbert Lutton, England ; James Murray McGillivray, Scotland ; William Thomson Mackie, Scotland ; Donald Stewart McLaren, Scotland ; Roderick Stewart Maclean, England ; Hugh Murdoch MacLeod, Scotland ; Robert Frederick Mahler, B.Sc., Austria ; Mary Herndon Marquis (*née* Potter), England ; Alastair Hugh Bailey Masson, Scotland ; George Morrison Maxwell, Scotland ; Ian Burnet Douglas Middlemass, Scotland ; James Alastair McCallum Millar, Scotland ; Ronald Alexander Millar, Scotland ; Margaret Elsie Mowat, Scotland ; Alan Ramsey Muir, England (with Honours) ; Marion Findlay Muir, Scotland ; Colin William Angless Murray, England ; James Elliot Murray, B.A. (CANTAB.), Scotland ; Joseph Ian Murray Lawson, Scotland ; Philip Roger Myerscough, England ; Joseph Newall, Scotland ; Dorinda Elizabeth Maude Nixon, N. Ireland ; Michael Francis Oliver, England ; Daniel Waugh Paterson, Australia ; James Reid Sinclair Paterson, B.Sc. (ST. ANDREWS), Scotland ; Sidney Leopold Paton, Scotland ; Mary Patten, England ; Annie Mackenzie Peach, Scotland ; Edward Chalcraft Pink, Scotland ; Thomas Brisbane Rankine, Scotland ; Muriel Richmond, England ; Horace David Ritchie, M.A. (GLASC.), B.A. (CANTAB.), Scotland ;

Julian Mervyn Roberts, England; Alexander Henry Mill Ross, Scotland; Ronald William Tullis Ross, Scotland; Lawrence Frederick William Rowe, England (*In absentia*); Alan Anderson Sharp, B.Sc., Scotland; Donald Shearer, Scotland; Leslie Simon, B.Sc., Scotland; Sylvia Rosemary Smith, England; Norman Thomas Speirs, B.Sc., Scotland; Margaret Stirling, Scotland (with Honours); William Brown Dickson Storie, Scotland; Norval Richard William Taylor, Scotland; William James Taylor, Scotland; Ian Howie Thomson, Scotland; James Noel Thorpe, England; Anne Catherine Wilson Walker, England; Peter James Walker, England; George Fordyce Watt, Scotland; Cameron Weymes, Scotland; Charles Brown Whittaker, Scotland; John David Wilkie, Scotland; James Graham Alexander Stuart Williamson, Scotland; Janet Pridmore Williamson, Scotland; Alastair Osborne Wilson, B.Sc., Scotland; Sydney Gordon Forbes Wilson, Scotland; Eric Walter Wright, England; Alfred Yarrow, England.

*Diploma in Public Health* :—James Borrowman, M.B., CH.B. (*In absentia*); John Dewar, M.B., CH.B.; Robert Gordon Drummond, M.B., CH.B.; William Alexander Glen, M.B., CH.B. (*In absentia*); Noel John Graham, M.B., CH.B. (*In absentia*); Hugh Wilson Horne, L.R.C.P.(ED.), L.R.C.S.(ED.), L.R.F.P. AND S.(GLASG.); James Kellock Hunter, M.B., CH.B.(GLASG.) (*In absentia*); Donald Page Lambert, M.B., CH.B. (*In absentia*); Archibald Alastair Cameron MacArthur, M.B., CH.B.; Lucy McFarlan, B.Sc.(ST ANDREWS), M.B., CH.B.; John Brown Menzies, M.B., CH.B.; Robert Mitchell, B.Sc., M.B., CH.B.; Hugh Pattinson, M.B., CH.B. (*In absentia*); James Arnold Petrie, M.B., CH.B. (ST ANDREWS); Patrick William Robertson Petrie, M.B., CH.B.; Guy Hamilton Scoular, M.B., CH.B.(GLASG.); John Harold Taylor, M.B., CH.B.; Robert Taylor, M.B., CH.B. (*In absentia*); William Campbell Wightman, M.B., CH.B. (*In absentia*).

*Diploma in Tropical Medicine and Hygiene* :—Basil George Hamilton Balfe, M.B., CH.B.; Ian Gordon Cameron, M.B., CH.B.; Jaroslaw Wiktor Czekalowski, M.B., CH.B. (LWÓW), M.D. (POLISH SCHOOL OF MEDICINE, EDIN.); William John Egerton Darling, M.B., CH.B.; John Gwesyn Davies, M.B., CH.B.; Francis Norman Macnamara, M.B., B.CH. (CANTAB.); Oswald Danvers Macnamara, M.B., B.CH. (CANTAB.); James Watson Martin, M.B., CH.B.; Nigel David Paton, M.B., CH.B. (ST ANDREWS); Sujoy Bushan Roy, M.B., B.S. (RANGOON); Syed Mohammad Shameem, M.B., B.S. (PATNA); Hereward Brunton Taylor, M.B., CH.B.; William James Toop, M.B., CH.B.

*Diploma in Medical Radiology* :—Gordon Campbell Griffiths, M.B., CH.B. (LIVERPOOL); Barney Hirschson, L.R.C.P. (ED.), L.R.C.S. (ED.), L.R.F.P. & S. (GLASG.).

*Diploma in Industrial Health* :—Nigel George Douglas, M.B., CH.B. (*In absentia*); James Donaldson Frame, M.B., CH.B.; Edward Ian Bruce Harvey, D.S.O., M.B., CH.B.; Gordon Hugh McCracken, M.B., CH.B. (*In absentia*); Dennis Malcolm, M.B., CH.B. (*In absentia*); John Millar, M.B., CH.B. (*In absentia*); James Scott, M.B., CH.B. (*In absentia*).

*Sister-Tutor Certificate* :—Agnes Isabella Campbell Bone; Jeannie Garrow Dingwall; Elizabeth Norrie Hughes; Elizabeth McRae Kerr; Eliza Jane Lockhart; Margaret Anne Robertson Macaskill; Williamina Tyrie McPherson; Helen Mitchell; Georgina Mulligan.

*The Polish School of Medicine at Edinburgh—The Degrees of Bachelor of Medicine and Bachelor of Surgery* :—Tadeusz Bobrowski, Emanuel Sylwester Brieger, Roman Burda, Jerzy Cyrankiewicz, Edward Czepulkowski



(*In absentia*), Lucyna Dylowna, Michal Dziemidko, Boleslaw Essen, Maria Grey, Szlama Grunstein, Tadeusz Heil, Borys Herszenhorn (*In absentia*), Lejb Hertz (*In absentia*), Edward Jozef, Jerzy Kucharski, Józef Łabędz-Kuderevich, Mordchel Margolis, Ludwik Mirabel (*In absentia*), Marian Nieswiatowski, Eugeniusz Orchel, Tadeusz Prorok, Aleksander Skowronek, Zdzislaw Szulec, Stanislaw Szutowicz, Erwin Turnheim (*In absentia*), Aleksander Wojciechowski.

*Faculty of Medicine: Awards of Scholarships, Bursaries, Prizes, etc.:*  
*The Cameron Prize in Practical Therapeutics*—Professor Neil Hamilton Fairley, C.B.E., D.S.C, M.D., F.R.C.P., F.R.S., Physician and Director of Special Research, Hospital for Tropical Diseases, London, in recognition of his work on the prophylaxis and treatment of Malaria. *The Ettles Scholarship and Leslie Medal, The Scottish Association for Medical Education of Women Prize, The Buchanan Scholarship in Obstetrics and Gynaecology, and The Dorothy Gilfillan Memorial Prize*—Eileen Vanora Haldane, B.Sc., M.B., CH.B. *The Vans Dunlop Scholarship in Clinical Therapeutics and Public Health*—Arthur Henderson Kitchin, M.B., CH.B. *The Murchison Memorial Scholarship in Clinical Medicine*—Constance Catherine Forsyth, M.B., CH.B. *The Ellis Prize in Physiology*—Helen Norman Duke, M.B., CH.B. *The Mouat Scholarship in the Practice of Physic*—Joseph Newall, M.B., CH.B. *The James Scott Scholarship in Obstetrics and Gynaecology*—Margaret Stirling, M.B., CH.B. *The Beaney Prize in Anatomy and Surgery, The Keith Memorial Prize in Systematic Surgery, and The Pattison Prize in Clinical Surgery*—Hugh Arnold Freeman Dudley, M.B., CH.B. *The Annandale Medal in Clinical Surgery*—Mary Stewart Somerville Barr, M.B., CH.B. *The Murdoch Brown Medal in Clinical Medicine*—Alastair Osborne Wilson, B.Sc., M.B., CH.B. *The Royal Victoria Hospital Tuberculosis Trust Medal*—Alastair Hugh Bailey Masson, M.B., CH.B. *The Wightman Prize in Clinical Medicine*—Arthur Henderson Kitchin, M.B., CH.B. *The Sir Robert Jones Prize in Orthopaedic Surgery*—Robert Buchan Duthie. *The Lawson Gifford Prize in Obstetrics and Gynaecology*—Daniel Waugh Paterson, M.B., CH.B. *The Wellcome Medal and Prize in the History of Medicine*—Graham Malcolm Wilson, M.B., CH.B.

An Address to the new Graduates was delivered by the Promotor, Professor James Rognvald Learmonth, C.B.E., M.B., CH.M., F.R.C.S. (ED.).

At a meeting of the Royal College of Surgeons of Edinburgh held on 29th July 1947, Mr James M. Graham, President, in the Chair, the following who had passed the requisite examinations were admitted Fellows: John Hunter Annan, M.B., CH.B. UNIV. EDIN. 1938; Paul Baer, M.D. UNIV.

MILAN, 1938, L.R.C.P. AND S. EDIN. (Triple), 1939; Charles Andre Bathfield, M.R.C.S. ENG., L.R.C.P. LOND. 1938; Ben Bellon, M.B., CH.B. UNIV. CAPE TOWN 1936; Meyer Berkowitz, M.B., CH.B. UNIV. WITWATERSRAND, 1936; Alexander Leonard Black, M.B., CH.B. UNIV. LIVERPOOL, 1938; Gavin Boyd, M.B., CH.B. UNIV. GLASGOW, 1936, M.R.C.O.G., 1941; Walter Standish Braidwood, M.B., B.CH., B.A.O. QUEEN'S UNIV. BELFAST 1938; Kenneth Cooke Burrow, M.R.C.S. ENG., L.R.C.P. LOND. 1938; Leonore Stanley Cooke, M.B., CH.B. UNIV. EDIN. 1939; Mary Doreen Daley, M.B., B.S. UNIV. LOND. 1937, M.D. UNIV. LOND. 1940, M.R.C.O.G. 1942; Richard Henry Dawson, M.B., B.S. UNIV. NEW ZEAL. 1940; William Hugh Ekin, M.B., CH.B. UNIV. CAMB.

1937; Herbert Samuel Gild, M.B., CH.B. UNIV. CAPE TOWN 1934; Aaron Isaac Goodman, M.B., CH.B. UNIV. MANCH. 1942; Isidore George Graber, L.R.C.P. AND S. EDIN. (Triple) 1942; George Kenneth Graham, M.B., B.CH., B.A.O. UNIV. DUBLIN 1929; Kenneth Edmund Guest, M.B., B.S. UNIV. DURHAM 1938; Richard Henry Hannah, M.B., CH.B. UNIV. EDIN. 1937; Duncan St Clair Lawson Henderson, M.B., CH.B. UNIV. GLASG. 1937; Peter Shaw Hollings, L.M.S.S.A. LOND. 1943; Robert Gwilym Hughes, M.B., B.CH. UNIV. WALES 1944; Jeremiah Hurley, M.B., B.CH. NAT. UNIV. IRELAND 1936; James Hutchison, M.B., CH.B. UNIV. GLASG. 1940; John Stewart Farrell Hutchison, M.B., CH.B. UNIV. GLASG. 1943; John Walker Sinclair Irwin, M.B., B.C.H., B.A.O. QUEEN'S UNIV. BELFAST 1937; Richard Evan Isaac, M.R.C.S. ENG., L.R.C.P. LOND. 1927; John Joyce, M.R.C.S. ENG., L.R.C.P. LOND. 1940; Darab Jehanghir Jussawalla, M.B., B.S. UNIV. BOMB. 1937; John Patrick Kelly, M.B., B.CH. UNIV. COLLEGE CORK 1943; Harold Felix Lowenthal, M.B., CH.B. UNIV. LIVERPOOL 1931; Philippa Mary Ludlam, M.B., CH.B. UNIV. EDIN. 1941; Brendan McCarthy, M.B., B.CH., B.A.O. UNIV. COLLEGE CORK 1940; Iain McLennan, M.B., CH.B. UNIV. GLASG. 1939; Stephen Madden, M.B., CH.B. UNIV. LEEDS 1938; Kenneth Lewis Marks, M.B., CH.B. UNIV. EDIN. 1941; Frederic John Charles Matthews, M.R.C.S. ENG., L.R.C.P. LOND. 1938; Douglas Mearns Milne, M.B., CH.B. UNIV. ABERDEEN 1940; David Gwyn Morris, M.R.C.S. ENG., L.R.C.P. LOND. 1940; Frederick Philip Morris, M.R.C.S. ENG., L.R.C.P. LOND. 1941; Maurice James Dewar Noble, M.B., CH.B. UNIV. EDIN. 1942; John Orr, M.B., CH.B. UNIV. EDIN. 1941; Frank Paulson, M.D. UNIV. MANITOBA 1934; L.M.C.C. 1935; Robert Edward Pow, M.D. UNIV. ALBERTA, 1943, L.M.C.C. 1943; Thomas Mackesy Prossor, L.R.C.P. AND S. EDIN. (Triple) 1940; Eric Rea, M.B., B.CH. QUEEN'S UNIV. BELFAST 1941; Harry Campbell Rose, M.B., CH.B. UNIV. WITWATERSRAND 1937; James McLean Ross, M.B., CH.B. UNIV. EDIN. 1938; John Young Walker Russell, M.B., CH.B. UNIV. EDIN. 1941; Chandrakant Gokaldas Saraiya, M.B., B.S. UNIV. BOMB. 1937, M.D. 1941; James Bruce Scott, M.B., CH.B. UNIV. ST ANDREWS 1937; Leslie Bertram Scott, M.B., B.S. UNIV. LOND. 1940; Thomas Sergeant, M.B., CH.B. UNIV. GLASG. 1941; James McGowan Shaw, M.B., CH.B. UNIV. GLASG. 1943; Ronald Thomas Simcox, M.R.C.S. ENG., L.R.C.P. LOND. 1933; Rama Virendra Prasad Sinha, M.B., B.S. UNIV. PATNA 1940; William Porteous Small, M.B., CH.B. UNIV. EDIN. 1942; Roland James Shand Smith, M.B., CH.B. UNIV. EDIN. 1935; Thomas Smith, M.B., CH.B. UNIV. GLASG. 1940; Victor George Springett, M.R.C.S. ENG., L.R.C.P. LOND. 1942; Mannie Stein, M.B., B.CH. UNIV. WITWATERSRAND 1942; Walter Henry Stephenson, M.R.C.S. ENG., L.R.C.P. LOND. 1936; Zakaria Taher, M.B., CH.B. UNIV. CAIRO 1934; Stanley Ferguson Thomas, M.B., B.S. UNIV. LOND. 1936; James Clark Walker, M.B., CH.B. UNIV. GLASG. 1938; John Watson, M.B., B.CH. UNIV. CAMB. 1938; Alistair Gordon Donald Whyte, M.B., CH.B. UNIV. ABERDEEN 1931; John Joseph Williams, L.R.C.P. AND S. IRELAND 1937; Robert Irvine Wilson, M.B., B.CH., B.A.O. QUEEN'S UNIV. BELFAST 1938.

*Higher Dental Diplomates*:—The following candidates having passed the requisite examinations were admitted Higher Dental Diplomates: Arthur Baker, L.D.S., R.C.S. EDIN. 1937; Bertie Cohen, B.D.S. UNIV. WITWATERSRAND 1942; Geoffrey Thomas Hutchinson, L.D.S., R.C.S. EDIN. 1939; Gerard Edward Bernard Moore, L.D.S. UNIV. LIVERPOOL 1939; William Morison, L.D.S., R.C.S. EDIN. 1939; Norman Lester Rowe, L.D.S., R.C.S. ENG. 1937.

THE examinations of the Board of the Royal College of Physicians of Edinburgh, the Royal College of Surgeons of Edinburgh, and the Royal Faculty of Physicians and Surgeons of Glasgow have just concluded at Edinburgh. The following passed the Final Examinations, and were granted the diploma of

**Triple  
Qualification  
Board.**

L.R.C.P. EDIN., L.R.C.S. EDIN., L.R.F.P. AND S. GLASG. on 18th July 1947:—  
David Kilpatrick Minto Allison, William Bain Balderston, Mary Elizabeth Barton, Robert Black, John Frederick Chacko, John Theodore Nelson Cole, John Crow, Thomas Lawrence Cook Dale, William Davidson, Maureen Margaret Devine, David Clark Drummond, Cecil Gibson Duncan, Sheila Margaret Forsyth, Samson Goldin, Samuel Healey Goodman, Donald Stewart Griffith, George Francis Wilkie Hossack, Matilda Yuille Dunbar Hutchison, William Jack, Leonard Kramer, Allan James Laidlaw, David Murray Lyon, Kenneth Ian Maclean, Hector McNeil, Blair MacTaggart, Mary Ann Mahoney, Herbert Lumley Matthews, Alistair Millar, Dwight Lionel Moody, Janet Queen Morton, Mary Cowan Penny, William Rose Plews, Doreen Sheila Ryan, Doreen Ramsay Cassels Scorgie, Alexander William Rose Thom, Norman Weiselberg, Margaret Louise Westwater.

## NEW BOOKS

*An Approach to Social Medicine.* By JOHN KERSHAW, M.D., D.P.H. Pp. 329. London: Baillière, Tindall & Cox. 1947. Price 15s

The title of this book is to be taken literally. It is concerned with the development of a particular attitude towards medicine and towards society. While every good practitioner is actively concerned with the development of medicine in relation to social life, too few have accepted the challenge that medicine must take an active part in the influencing of social activities in the interests of human well-being.

In order to make an appraisal of the disorders and disharmonies from which it suffers, Dr Kershaw reviews the anatomy and physiology of society. He next discusses the developments of the major branches of medicine in relation to social activities. Finally, he considers some of the more urgent health problems which society has created. Social medicine is a philosophy of health, and the last chapter appropriately deals with the human and social instruments of that philosophy.

In spite of its theoretical preoccupations this is a practical work, and is recommended not only to all medical men but also to those who claim to be responsible citizens, for it is to this larger audience that the author makes his appeal. The succinct and necessarily dogmatic review of such a wide territory satisfies a very real need of the average doctor, and the more enquiring are catered for in an excellent and ample bibliography.

*Case Studies in the Psychopathology of Crime.* By BEN KARPMAN, M.D. Pp. viii+738. Washington: Medical Science Press. 1947.

This is the second volume of a series of studies dealing with the psychopathology of criminals. The four case records are submitted in great detail, and for the most part in the words of the criminal. This present volume deals exclusively with sex crimes, and the hope is expressed that the book may serve as a reference source for research in criminal material. One case treated by psychotherapy has shown no repetition of crime behaviour, and it is suggested that in some instances at least criminality may be regarded as a particular form of psychic disease.

While the volume is of considerable interest and shows evidence of much painstaking work, yet it could have been made much more readable and informative if the material had been curtailed and summarised.

*Group Psychotherapy.* By J. W. Klapman, M.D. Pp. vii+374. London: Messrs William Heinemann. 1947. Price 21s. net.

This book is published at an appropriate time because Group Psychotherapy, largely as a result of the difficulty of providing individual treatment during the war years, has attained considerable popularity. Although not known by the name Group Psychotherapy, yet such forms of treatment have been employed from comparatively early times, and it is probable that Mesmer's success was due to such group methods. This work has now, however, been put on a more organised basis and the author credits Dr J. H. Pratt, who worked particularly with tuberculous patients, as being the founder of this method. As more specifically applied to psychiatry, Moreno labelled the method psychodrama, and in the first place applied it to children, so that they might be encouraged to act out their fantasies.

This book details how the principles of Group Psychotherapy might be applied to all grades of nervous and mentally ill patients, and it gives an interesting report of the work which has been already accomplished. The author, too, is careful not to claim too much, and recognises that the method owes a good deal to the ancillary aids which are part and parcel of hospital treatment.

*Atlas of Histopathology of the Skin.* By G. H. PERCIVAL, A. MURRAY DRENNAN and T. C. DODDS. Pp. viii+494, with 376 photomicrographs in colour. Edinburgh: E. & S. Livingstone Ltd. 1947. Price 75s. net.

In this book the histopathology of the various skin diseases has been portrayed in a most excellent series of colour photomicrographs taken by the Finlay process. A clinical classification of the conditions has been adopted and, according to the authors, "they have been grouped according to the type of primary cutaneous change by which they are characterised and not according to their ætiology, known or presumed. This method has been employed for practical reasons, for skin diseases are much more individually distinct in the clinical aspect than in their pathology, and the ætiology is in so many cases obscure."

In general a series of reproductions illustrating a histological section of a lesion from a low to a high magnification has been given. The low-power illustrations are of use in giving a general anatomical picture of the condition, so necessary in dealing with a cutaneous lesion, and under the higher magnifications the different types of cell and tissue change can be readily identified. Each is accompanied by a brief but informative caption. The letterpress, although not lengthy, gives a succinct and well-balanced description of the pathology of the various conditions described. The illustrations from the beautiful work of Mr Dodds are of a very high standard and have on the whole been well reproduced, only one or two out of the 376 showing a slight deviation in registration of the half-tone blocks.

This is a unique publication, of value to the dermatologist and pathologist, and is truly fitting as the first from the Department of the first Chair of Dermatology in Great Britain, to the founder of which, the late Sir Robert Macvitie Grant, the book is dedicated.

*Renal Diseases.* By E. T. BELL. Pp. 434. With 119 illustrations. London: Henry Kimpton. 1946. Price 35s. net.

This monograph embodies the results of studies and observations on renal diseases encountered over a twenty-five years period. The subject matter is predominantly pathological; clinical manifestations are discussed in correlation with the pathological findings.

The illustrations are excellent and cover the macroscopic and microscopic appearances of all types of kidney lesion. There are four plates in colour. The chief clinical findings of the cases illustrating the diseases are given in tabular form—12 pages with 186 cases of "chronic azotæmic glomerulonephritis" demonstrate the careful labour expended by the author. Each section ends with a complete list of references.

Valuable chapters on developmental anomalies, surgical conditions of the kidneys, diseases of the blood vessels, hypertension, diseases of the kidney related to metabolic disorders, and extrarenal azotæmia add to the merit of a reference book of high quality.

*Medical Disorders of the Locomotor System, including the Rheumatic Diseases.*

By ERNEST FLETCHER, M.A., M.D.(CANTAB.), M.R.C.P.(LOND.). Pp. xii+625, with 262 illustrations. Edinburgh: E. & S. Livingstone Ltd. 1947. Price 45s. net.

The author has set out to bring under one cover the available information on the subject of the medical locomotor diseases. In this he has succeeded admirably. Much prominence has been given to the rheumatic disorders because, as he says, so rightly, they are well recognised the world over as a social scourge and a national problem. A chapter is devoted to the incidence and prevalence of adult rheumatism bringing home forcibly to the reader the magnitude of the problem.

The subject is approached from the viewpoint of regional anatomy and physiology which provides an excellent background from which to study the clinical aspects of the problem.

The author has been fortunate in enlisting the aid of such an able team of collaborators. In each section a comprehensive review of the subject is given and a useful bibliography of the more recent literature.

Dr Fletcher is to be congratulated on his production which will undoubtedly prove exceedingly popular not only with the specialist in rheumatic disorders but more especially with the general physician. It is beautifully produced, easy to handle and well illustrated by a series of really excellent photographs.

## NEW EDITIONS

*The Normal Encephalogram.* Second Edition. By LEO. M. DAVIDOFF, M.D., and CORNELIUS G. DYKE, M.D. Pp. 232, with 155 illustrations. London: Henry Kimpton. Price 27s. 6d. net.

The first edition of this work was favourably received in the *Journal* shortly before the war, and it is a pleasure to welcome this volume which has been thoroughly revised notwithstanding the heavy burden falling on the remaining author after the untimely death of Dr Cornelius G. Dyke in 1943. He has fulfilled his task uncommonly well, managing to evaluate the study on the basis of a greatly augmented experience, indeed the understanding of the encephalogram has progressed enormously in the intervening years, a fact which is clearly reflected in the enormous numbers of cases which have been seen.

The five subdivisions of the book are well thought out, the different aspects clearly stated, and unnecessary repetition carefully avoided, all making for easy reference and always giving an authoritative and convincing impression of this important aspect of neurological investigation. Without exception the engravings are magnificent, a fact that is all the more impressive to the reader who for so long has been accustomed to austerity productions. Of course these reproductions are the very essence of the work, as without them the text would soon be incoherent. There is a hint in the preface of a further volume on *The Abnormal Encephalogram*, the publication of which would place all English-speaking neurologists still further in the author's debt.

*Pre-operative and Post-operative Treatment.* MASON and ZINTEL. Second Edition. Pp. xiv+584, with illustrations. Philadelphia and London. W. B. Saunders & Co. 1946.

As the authors remark in the preface to this second edition, there has been during recent years a greatly increased emphasis upon the importance of carefully planned

and rationally applied pre- and post-operative treatment. The modern surgeon has need therefore of a reliable guide to pre- and post-operative measures and the book under review can be heartily recommended. It is the most complete and satisfying book of its kind that the reviewer has seen. The subject is dealt with on general lines in Part I, under such chapter headings as "Conditions Affecting the Operative Risk," "Pre- and Post-operative care of the Surgical Patient with Diabetes, Shock, Water-balance, etc." while in Part II a regional arrangement is adapted—the pre- and post-operative care of patients with Hyperthyroidism, Gall-Bladder Disease, Disease of the Colon and Rectum, etc., etc.

To be critical on one point, the recommendation that femoral vein ligation should be done on all patients with deep venous thrombosis might be questioned.

*Minor Surgery.* By CECIL FLEMMING. Twenty-third Edition. Pp. 406, with 209 illustrations. London: J. & A. Churchill.

This is the well-known handbook first written by Heath in 1861, and edited since then by Pollard, Davies and Williams in turn. Mr Flemming, like all his predecessors, is a surgeon at University College Hospital, and his thorough revision of the book for this edition brings it completely up-to-date and should enhance its reputation. It contains a wealth of detailed information about the minor surgical procedures with which all students and doctors should be familiar.

*Libido and Delusion.* By LOUIS S. LONDON, M.D. Second Edition. Pp. xi+259. Washington, D.C.: Mental Therapy Publications. 1947. Price \$3.50.

This book is said to contain the essentials of psychiatry and psycho-analysis, but actually this is very far from being the case. The material is presented entirely from a superficial psycho-analytic aspect and it is entirely unconvincing. The cases are reported briefly and no account whatsoever is given of the social and environmental backgrounds. Many of the statements are entirely dogmatic and without adequate foundation. It is stated, for instance, that fifty sessions are required to make a diagnosis of schizophrenia and that the differentiation between schizophrenia and manic depressive states may take even longer. That is only one example of the rather uninformed attitude of the author. It is impossible, even with the best will in the world, to find any justification for a book of this type. One hundred pages are devoted to the analysis of a case of schizophrenia in 353 sessions, and even at the end of that period it is admitted that the case was not a therapeutic success.

*Gas and Air Analgesia.* By R. J. MINNITT, M.D., D.A. Third Edition. Pp. vii+80, with 19 illustrations. London: Baillière, Tindal and Cox. 1947. Price 5s.

Dr Minnitt has for years been the recognised leader of the crusade for painless childbirth. His theories have been backed by sound practical methods evolved from wide experience. This excellent booklet is an authoritative exposition of the author's technique which is the standard one recommended by the Central Midwives Board.

*Notes on Clinical Laboratory Methods.* Standing Committee on Laboratory Methods, University of Glasgow. Fifth Edition. Pp. 95. Glasgow: John Smith and Son. 1947. Price 3s. 6d. net.

This small volume covers all the practical work which the medical student is required to do in the ward side-room. It is a detailed summary of practical procedures which have stood the test of time, and they are briefly and lucidly explained. It contains no superfluous matter and one is safe to say that every medical man should know the whole of its contents.

The statement (p. 51) that "several c.c. of blood" are required for blood grouping and compatibility is a little generous, and the use of the word "strong" where "concentrated" is meant is rather unfortunate. Otherwise the text is remarkably free from error. It is a book which can be confidently recommended.

# BOOKS RECEIVED

- SHERRINGTON, Sir CHARLES, O.M. The Integrative Action of the Nervous System. 1947 Edition entirely reset. (Cambridge University Press, Cambridge) 25s. net.
- PLESCH, JOHN. Blood Pressure and its Disorders, including Angina Pectoris. Second Edition. (Baillière, Tindall & Cox, London) 21s. net.
- HILL, HARRY, F.R.S.A.N.I., A.M.I.S.E., F.S.I.A. Pasteurisation. Second Edition. (H. K. Lewis & Co. Ltd., London) 21s. net.
- TRUETA, JOSEP, M.D., HON. D.S.C.(OXON.), BARCLAY, ALFRED E., O.B.E., D.M., F.R.C.P., F.F.R., F.A.C.R., DANIEL, PETER M., M.A., M.B., FRANKLIN, KENNETH J., D.M., F.R.C.P., PRICHARD, MARJORIE, M.L., M.A. Studies of the Renal Circulation. (Blackwell Scientific Publications, Oxford) 25s. net.
- Edited by NEWTON, C. T. HAND, D.S.O., M.D., F.R.A.C.P., F.R.C.S.(EDIN.). The Christchurch Hospital Medical Manual. Second Edition. (N. M. Peryer Ltd., Christchurch, New Zealand) —
- NICOLE, J. ERNEST, O.B.E., L.M.S.S.A., D.P.M.R.C.P. AND S. Psychopathology. Fourth Edition. (Baillière, Tindall & Cox, London) 15s.
- MOODIE, WILLIAM, M.D., F.R.C.P., D.P.M. The Doctor and the Difficult Adult. (Cassell & Co. Ltd., London) 15s. net.
- EWART, E. D. A Guide to Anatomy. Sixth Edition. (H. K. Lewis & Co. Ltd., London) 25s. net.
- THORPE, WILLIAM VEALE, M.A.(CANTAB.), PH.D.(LOND.). Biochemistry for Medical Students. Fourth Edition. (J. & A. Churchill Ltd., London) 18s.
- JELLINEK, S., M.D. Dying, Apparent-Death and Resurrection. (Baillière, Tindall & Cox, London) 10s. 6d.
- KOLFF, W. J., M.D. New Ways of Treating Uræmia. (J. & A. Churchill Ltd., London) 10s. 6d.
- BURN, J. L., M.D., D.HY., D.P.H. Recent Advances in Public Health. (J. & A. Churchill Ltd., London) 25s.
- BRAIN, W. RUSSELL, D.M.(OXON.), F.R.C.P.(LOND.). Diseases of the Nervous System. Third Edition. (Oxford University Press, London) 37s. 6d. net.
- COCHRANE, R. G., M.D., CH.B.(GLAS.), F.R.C.P.(LOND.), D.T.M. AND H.(ENG.). A Practical Textbook of Leprosy. (Oxford University Press, London) 42s. net.
- MOLLER, KNUD O. Parmakologie. (Benno Schwabe & Co. Basel) Gebunden Fr. 48
- Edited by REESE, H., M.D., MASTEN, MABEL G., M.D., LEWIS, NOLAN, D.C., M.D., BAILEY, PERCIVAL, M.D. The 1946 Year Book of Neurology, Psychiatry, and Neurosurgery. (The Year Book Publishers, Chicago) \$3.75.
- GOLDBERG, MORRIS. English-Spanish Chemical and Medical Dictionary. (McGraw-Hill Book Company Inc., London) 50s.
- SCOTT, WILLIAM ALBERT, B.A., M.B., F.R.C.S.(CAN.), F.R.C.O.G.(ENG.), and VAN WYCK H. BROOKFIELD, B.A., M.B., F.R.C.S.(CAN.), F.R.C.O.G.(ENG.). The Essentials of Obstetrics and Gynecology. (Henry Kimpton, London) 27s. 6d. net.
- HOWELL, Wing-Commander EDWARD, O.B.E., D.F.C. Escape to Live. (Longmans Green & Co., London) 8s. 6d. net.
- BOAS, ERNST P., M.D. Treatment of the Patient Past Fifty. Third Edition. (The Year Book Publishers Inc., Chicago) \$5.75
- Edited by DUNCAN, GARFIELD G., M.D. Diseases of Metabolism. Second Edition. (W. B. Saunders Company, London and Philadelphia) 60s. net.
- LICKLEY, JAMES DUNLOP, M.D. An Introduction to Gastro-Enterology. (John Wright & Sons Ltd., Bristol) 8s. 6d. net.
- MCALLISTER, JOSEPH B., S.S., PH.D. Ethics. With Special Application to the Nursing Profession. (W. B. Saunders Co., London and Philadelphia) 14s. net.
- BELL, E. T., M.D. A Text-Book of Pathology. Sixth Edition. (Henry Kimpton, London) 50s. net.
- Edited by CECIL, RUSSELL L., A.B., M.D., SC.D. A Textbook of Medicine (by American Authors). Seventh Edition. (W. B. Saunders Co., London and Philadelphia) 50s. net.
- WHARTON, LAWRENCE R., PH.B., M.D. Gynecology, with a Section on Female Urology. Second Edition. (W. B. Saunders Co., London) 50s. net.
- BEAUMONT, G. E., M.A., D.M.(OXON.), F.R.C.P., D.P.H.(LOND.), and DODDS, E.C., M.V.O., D.S.C., PH.D., M.D., F.R.C.P., F.R.I.C., F.R.S.(EDIN.), F.R.S. Recent Advances in Medicine. Twelfth Edition. (J. & A. Churchill Ltd., London) 21s.
- ETHEREDGE, MAUDE LEE, M.D., D.P.H. Health Facts for College Students. Fifth Edition. (W. B. Saunders Company, London) 12s. 6d. net.
- CRAWFORD, A. MUIR, M.D., F.R., F.P.S.G. Materia Medica for Nurses. Sixth Edition. (H. K. Lewis & Co. Ltd., London) 5s. 6d. net.

# Edinburgh Medical Journal

August 1947

## TUBERCULOUS INFECTION AND DISEASE OF THE LUNG IN CHILDHOOD \*

By CHARLES McNEIL, M.A., M.D., F.R.C.P.Ed. & Lond.

THIS is a large subject, and as an opening for discussion will be dealt with on broad lines: giving an account of the present prevalence of the disease in children; describing the general pathological and clinical features of the successive stages of infection and disease in the lungs; and finally discussing the present measures of control and the prospects of their improvement.

PERSPECTIVE.—Some preliminary remarks may assist in focussing the subject. In children, infection is received almost entirely inside the home, being passed to the children from the parents or elders in the intimate contacts of family life. A French medical aphorism about syphilis is equally true of lung tuberculosis: "it is shared between father, mother and children like the daily bread." When infection occurs in the lung of the child, it may be arrested leaving small and permanently healed lesions. But again, and this is common in the infant and younger child, the first infection may quickly pass into active disease, either in the lung itself or beyond; and is then nearly always fatal. This home and familial infection of children by tuberculous adults, although much diminished since the discovery of the infective agent by Koch in 1882, is still widely prevalent. Cases of open tuberculous disease in adults, undetected or diagnosed, constitute a reservoir or pool of infection; and it is the size and control of this reservoir of adult disease that determines the amount of infection and disease of the lung in children. Further it is still a reasonable hypothesis, although not proved nor accepted by all, that this reservoir of adult contagion is mainly filled up again by adolescents who have received their infection in childhood and in whom a long dormant interval has intervened between the initial infection and the appearance of active disease. Whether this hypothesis is true or not, it is true to say of tuberculous disease in man that its persistence and prevalence among the communities of mankind for many centuries is because of its easy transmission from one generation to the next in the intimate associations of parents and children.

\* Read at a meeting of the Medico-Chirurgical Society of Edinburgh on 15th January 1947.



Koch's discovery of the tubercle bacillus in human sputum has given medicine a powerful weapon of control. But our bacteriological knowledge has not been matched by an equal clinical skill in early diagnosis, and many children are still infected because of the hidden and symptomless character of the early stages of the disease in their parents. Further, even when the disease is unmasked in a parent, we cannot apply the same thorough efficiency in removal of the parent carrier or in segregation of the child contacts, as can be used in other infections, without disruption of the family. Lastly, in the child and especially in the first five years of childhood, successful control requires the detection of infection in its first phase and its arrest at that stage, because the spread of disease in the lung or beyond it causes in most cases intractable and fatal illness.

In spite of these formidable difficulties in the control of pulmonary tuberculosis both in the adult and the child, the steady fall of cases in the adult has been accompanied by as great a fall of fatal cases in the child. But this reduction in child tuberculosis is largely due to the *negative effect* of there being a much smaller number of open cases of lung tuberculosis in parents and elders. There has thus been a smaller reservoir of tuberculous sputum, and therefore a smaller ration of infection for dispersion among British families; also this reservoir has been brought under better control by the increasing efficiency of a special medical service. The reduction in child tuberculosis (as shown by death-rates) is not due to any extent to *positive success* in controlling pulmonary infection in the child, either by arresting it at the first stage or by curing the local or general types of disease that may follow.

From this argument the crucial question emerges—Can more be done to arrest tuberculous infection of the lung in children at its first lodgment, known as the primary phase?

#### STATISTICS OF PULMONARY TUBERCULOSIS IN ADULT AND CHILD

A few figures will show at a glance how steady and how rapid has been the fall in tuberculosis death-rates in the last eighty years. These rates are shown in three categories—"all forms," respiratory,

TABLE I  
*Tuberculosis Death-Rates (per 100,000 population)*  
Scotland 1866-1943

Period or Year.	All Forms.	Respiratory.	Other Forms.
1866-70 . . .	382	270	112
1901-05 . . .	218	148	60
1921-25 . . .	117	81	36
1936-40 . . .	74	56	18
1943 . . .	83	62	21

and "other forms" (*i.e.* other than respiratory); they include all ages of life; they are quinquennial averages except for the last figures for 1943.

The figures have risen since the onset of the recent war; but this rise is likely to be temporary as it was during the 1914-18 war. Note that in these death-rates, which include all forms of the disease and all ages, the respiratory rates greatly exceed those from the other clinical types consistently throughout the period (2 to 1, or 3 to 1). But the next table, which gives the Scottish deaths in special categories and in 5-year age periods from birth to 25 years, shows in the three age periods of childhood a reversal of this preponderance of respiratory deaths over the "other forms" group. The explanation of this childhood reversal from the adult and also the "all ages" figures in Table I is important, and as it has an important bearing on the problem

TABLE II  
*Tuberculosis Deaths, Scotland 1943. Clinical Categories and Age Periods*

	Age Periods.					
	0-5	5-10	10-15	15-20	20-25	All Ages.
<i>Category—</i>						
All Types . . . . .	348	135	141	495	537	3959
Respiratory . . . . .	<u>73</u>	<u>35</u>	<u>45</u>	<u>340</u>	<u>445</u>	<u>2976</u>
Other Forms (Total) . . . .	<u>275</u>	<u>100</u>	<u>96</u>	<u>155</u>	<u>92</u>	<u>983</u>
<i>Other Forms—Specified Type—</i>						
Abdominal . . . . .	19	10	7	11	16	109
Meningeal . . . . .	215	73	72	101	25	545
Disseminated . . . . .	38	15	14	28	37	193
Et cetera . . . . .	3	2	3	15	14	136

of prevention and control of the disease in childhood, it will be discussed later.

The underlined figures in Table II show a *striking preponderance of deaths from "other forms" over the respiratory up to fifteen years, and then a sudden and decisive reversal of this in the 15-20 period*, and the continuation of this respiratory preponderance in the adult life-period.

The group "other forms" is broken up into abdominal, meningeal, disseminated, and a miscellaneous group named "et cetera," including osseous, genito-urinary, glandular, etc. The contribution of abdominal tuberculosis to these deaths is never large and remains fairly steady throughout life. But meningeal tuberculosis is at its high peak in the first age period (0 to 5 years) then drops to a high plateau until the 15 to 20 period, and thereafter becomes small. The same general trend is seen in the disseminated group but at a much lower level.

These are complicated and rather bewildering figures, but they have definite pathological explanations which arise out of the differing

pathological processes and behaviour of tuberculous disease in the human body from infancy through childhood to adolescence. And these pathological explanations give an answer to an important question—in this preponderance of “other form” tuberculosis deaths over the respiratory deaths up to fifteen years, *what is the allocation of these “other forms” deaths to original respiratory infections (that is human) on the one hand, and on the other to original abdominal infections (that is bovine)?*

The explanation is as follows. Meningeal and disseminated tuberculosis are widespread disseminations from three sites of original infection and local disease, the tonsils and throat, the lungs, and the intestinal tract. The extensive post-mortem studies of Agnes Macgregor in Edinburgh, and Blacklock in Glasgow, have shown that these fatal types of disseminated tuberculosis are derived from an original site in the tonsils and throat in about 5 per cent., from the lungs in about 63 per cent., and from the intestinal tract in 32 per cent.; that in most of these disseminations the primary focus of infection and disease is small and has not caused illness recognised by symptoms or by searching clinical and X-ray examination. With this reliable pathological guidance, the allocation of these large numbers of fatal cases of disseminated tuberculosis in childhood can now be made; and it is clear that about two-thirds can be classed as original respiratory infections, and about one-third as original abdominal infections. It is now clear that in childhood the small number of respiratory deaths shown in Table II is deceptive, and that in childhood as in adolescent and adult life there is an actual and overwhelming preponderance of respiratory infections. But in childhood most of these respiratory infections cause death, not by local disease, but by the effects of dissemination: while after the age of about twenty years, dissemination becomes much less common and death is caused by progressive tuberculous disease of the lung itself.

#### PATHOLOGICAL PROCESSES IN THE LUNG

It will be sufficient to give a short and condensed description of the principal phases of tuberculous disease of the lungs in childhood. These, although not essentially different from those in the adult, show variations which are of great clinical importance, and are still more important in considering the problem of control. The first stage of infection shows a complex of lesions—the initial small caseous focus in the lung and usually sub-pleural, a track of tuberculous lymphangitis from the primary focus across the lung, and a group of tuberculous glands within the hilum of the lung and along the main bronchus and trachea: this is called the primary complex or first stage. In the majority of cases this first stage passes unnoticed, causing neither illness nor detectable signs in the thorax (although it may do both); but its hidden existence is revealed, although the site can only be

surmised, by a positive skin tuberculin reaction. There are three possible consequences: arrest and healing; extension of local disease in the primary lung focus or root-glands; and spread of infection by dissemination causing meningitis, general miliary tuberculosis, osseous tuberculosis, renal tuberculosis, etc. Local extensions in the lung, if they proceed to the formation of cavities, are progressive and fatal; but pleurisy with effusion, limited hilar tuberculosis and that uncommon massive pneumonia called epituberculosis are curable. Among the group of disseminations, which are much more numerous than the local group, meningitis and miliary tuberculosis are nearly always fatal. In the child, and especially in the infant and young child, this fatal dissemination generally takes place soon after (a few weeks or months) the original infection. These progressive and fatal types of tuberculous disease within the lung and beyond it present urgent and difficult clinical problems, and interesting and important pathological ones, but they are seldom capable of arrest or cure. It is only at the first stage and before local or general extension has taken place that we can hope to take effective measures of control. The problem of control centres in the detection and arrest of the primary stage—a disease complex limited to a small focus in the lung and to a group of tuberculous glands in the root and mediastinal glands with an intervening tuberculous track across the lung. Although we have in the skin tuberculin tests an easy and certain detector of this primary stage, our measures of arrest and control are still ineffective. Nevertheless these local tuberculin tests widely applied can give information approximately accurate of the extent of primary stage infections of the lungs in childhood, just as the study of the Registrar-General's figures of all tuberculosis deaths in childhood, with the adjustment of these figures by ratios of original sites derived from pathological studies, can give us an approximate total, year by year, of the number of fatal cases of local lung extension and of widespread dissemination. By tuberculin skin tests, we can at least measure the extent of early tuberculous infection of the lung in childhood as something distinct from that of fatal tuberculous disease. It is valuable to know the size of the preventive problem that has to be dealt with.

#### PREVALENCE OF PULMONARY TUBERCULOUS INFECTION

Fleming has recently published the results of Mantoux tuberculin tests on over 4000 Glasgow hospital children between 1938 and 1942. These results are compared with my findings in an Edinburgh series of 541 tuberculin tests with a modified Pirquet technique. The Edinburgh investigation was done between 1910 and 1912. The age groups are similar although not identical.

These percentages of positive tuberculin reactions in Scottish children show three points: the characteristic rise in the frequency of infection from infancy to adolescence that has been shown in such

investigations all over the world since V. Pirquet introduced his test in 1906; the considerable fall in incidence over a period of thirty years; but the third point is most significant—the still high prevalence of tuberculous infections in Scottish children as shown in this large scale investigation in Glasgow and with the most delicate Mantoux test.

### MANTOUX TEST

The Glasgow older age group is 10-13 years. It is roughly estimated that the full age group 10-15 years in this social sample would give 50 per cent. positive reaction. The child population in Scotland between 10 and 15 years in 1943 was 413,000. In a representative sample of Scottish children, urban and rural, at these ages the percentage of positive reactions would be smaller than in the Glasgow sample; and, if it be taken as 25 per cent. as a rough approximation, this would mean that about 103,000 Scottish children

TABLE III  
*Cutaneous Tuberculin Tests in Scottish Children*

	Age Groups and Percentages of Positive Reactions.		
	0-5 years (Edin.), 0-4 years (Glasg.).	5-10 years (Edin.), 4-10 years (Glasg.).	10-15 years (Edin.), 10-13 years (Glasg.).
Edinburgh 1910-12 (McNeil)	31.0% (200)	42.7% (152)	60.8% (189)
Glasgow 1938-42 (Fleming)	9.3% (3045)	31.6% (1094)	44.8% (301)

(Numbers in brackets are total tests in each group.)

have a primary focus of tuberculous infection. But we have still to distribute these primary infections between the three primary sites, the tonsils and throat, the lungs, and the intestinal tract, and between the two sources of infection, human and bovine. If we are to use again the guidance of post-mortem examinations in Edinburgh and Glasgow, we must remember that primary site infections in the throat and intestinal tract may never proceed to actual disease and much less to fatal disease and yet will give positive tuberculin reactions. Therefore the calculation of the number of lung infections in this approximate 100,000 positive reactions in Scottish children between 10-15 years can be only a rough and loose one, but a figure of 50,000 is suggested. Without guessing at numbers it is certain that in Scotland to-day the number of children between puberty and adolescence carrying a primary tuberculous complex in the lung is very large. And that in the majority of cases, these children have received their infection at home from father, mother or other relative. Many, perhaps most, of these primary lung infections are already or will be arrested and permanently healed. But a substantial number will evolve later into

the active lung disease of adolescence and early adult life and will help to fill again the reservoir of infection for the new generation of children.

### THE CONTROL OF TUBERCULOUS INFECTION AND DISEASE OF THE LUNG IN CHILDHOOD

The problem of control has two sides: one concerns the adult, the other the child. In the case of the adult the requirements of effective control are the early diagnosis and treatment of the disease; his segregation from his fellow-workers; and his separation from his children, or if he remains at home, the best possible measures for the protection of the children. This side of control, already a well organised service, has had a setback during the war, but it will be raised again to its former efficiency and will become still more efficient. It is the initiation and perfection of the specialist tuberculosis service, assisted no doubt by the raising of the general standards of life at home and at work, that has accounted for the great reduction of tuberculosis deaths in adults and children during the last sixty years. Sixty years ago Robert Philip was the pioneer of the organised attack upon tuberculosis in establishing a tuberculosis dispensary in Edinburgh, and for fifty years, both in ideas and in their translation into action, he was a leader in the campaign. The introduction of mass radiography promises to be a powerful weapon by securing the discovery of many more cases of disease at an early or even pre-contagious stage.

The control of pulmonary tuberculosis in the child has lagged far behind; indeed an organised service of positive control has not yet been built up. The peculiar behaviour of infection and of disease in the lung of the child is either not recognised or not yet applied in the tuberculosis service. In the adult the control service attacks *the disease*, in the earliest possible stage; but in the child the attack if it is to be effective must be on the *early infection* and before disease of the lung has begun or dissemination occurred. The outbreak of disease in the adult is determined by the discovery of the bacillus in the spit, and this fact is notified. The occurrence of infection in the child can be determined with equal certainty by a tuberculin test. This test is still largely reserved for differential diagnosis in *the illnesses of children*. It has been used in many clinical investigations to give information about infection in healthy children, but it has not been used as a routine practice in a control service for children. The use of the tuberculin test as a diagnostic of infection has of course been urged again and again by Philip and many others, and recently Gaisford has suggested the use of the Mantoux test in all children under two years. Surely the time has come for serious consideration of the widespread employment of one of the simpler cutaneous tests in school children and even in those attending welfare clinics. The information so gained would be of great value in prompting immediate

further clinical examination to determine the site of infection and necessary action, and in continued supervision of positive reactors. The prevalence of tuberculous lung infection as shown by the mass use of the tests in Edinburgh and Glasgow justifies this attempt to obtain a census of tuberculous infection in childhood, and especially in school children.

### INFECTION AND DISEASE IN CHILDREN IN A TUBERCULOUS COMMUNITY (PAPWORTH)

In the Papworth Village Settlement under the superintendence of the late Sir Pendrill Varrier-Jones, there has been for nearly thirty years a community of families where one or both parents have had active lung tuberculosis, and where their children are exposed to infection in the ordinary routine of family life. Both the parents and the children have been under close medical observation, and recently Brieger has published the results of tuberculous infection and disease in the children as shown by tuberculin skin tests and clinical and X-ray examinations.

Of 108 children born in the village and under different circumstances of contact, the infection rate, determined by the Moro ointment test, was 56·8 per cent. The incidence of tuberculous disease in the thorax, shown by clinical and X-ray examinations, was as follows: 55 children (51 per cent.) showed no clinical or X-ray lung lesions; 53 (49 per cent.) showed by the same examinations evidence of "primary complex" lesions, including two transient perifocal reactions; there were *no cases of active lung disease and no cases of dissemination* (meningeal or miliary). This is a remarkable result; showing that among about 100 children under varying conditions of contact and with an infection prevalence of about 60 per cent., it was possible to locate the primary stage lesions in the lung in 49 per cent.; that during the stay of the children in the village none of these primary lesions extended locally in the lungs as progressive disease, and none produced a fatal dissemination.

The results in the other group of 151 children admitted to Papworth, after varying periods of contact with sputum-positive parents in their previous homes, were not so good. Primary lesions were found or developed in 101 children (66·9 per cent.); progressive lung disease of childhood or adult type developed in 13 cases (8·6 per cent.). But again there were no fatal disseminations during residence in Papworth.

LESSONS OF PAPWORTH.—What is the application to the general community of this experience of children living in "tuberculous" homes, where the danger of infection is known, and the occurrence of pulmonary infection and pulmonary lesions ascertained by a medical service of control and supervision?

The results seem to be very good, and to encourage the hope that similar results might be got in the general community, if similar

methods were used. But it must be noted that the housing and economic conditions of the families in Papworth were good, and the danger of infection was known and thereby the risks of contagion were reduced.

The conditions in the general community for the control of pulmonary tuberculosis are not so favourable. In Papworth the control service starts with the recognised case and from that point there is begun not only adequate treatment of the adult but strict surveillance of the home and of the rest of the inmates, including subsequent children. In the general community, the adult cases are hidden in the mass of homes; often they are highly infective to their household long before they are detected, and have already infected and produced fatal disease in the children; even after detection an efficient service of diagnosis, examination and supervision for the children is lacking.

But the service of control so effective in Papworth is not too elaborate as regards the children; there are no child preventoria there, and the homes are left intact. To get the principles of Papworth applied to the general community of children exposed to tuberculous infection in their homes, there must be an efficient service of diagnosis of infection by tuberculin tests, and of supervision of the homes and children where positive reactors are found. The existing tuberculosis service has not sufficient medical staff to undertake this additional work, but the necessary medical staff can surely be found in the family doctor. His sphere of work is inside the home, he enjoys the confidence of the parents, he is well able to carry out the simple and quite reliable skin tests. Without going into detail, the outline of the organised control service of lung tuberculosis in childhood should be the widespread use of the simpler cutaneous tests carried out at home, in welfare and school clinics; the keeping of a register of positive reactors in the offices of the tuberculosis service; the careful supervision by family doctors of homes and of all their inmates, child and adult, from which these positive tests are obtained; and the full use of the expert clinical experience of lung tuberculosis that is to be found in children's hospitals. The new medical regional service with its ideal of co-ordination has a great opportunity of creating such a service for children, in which general practitioners, child welfare and school medical officers, and children's physicians would all play their part under the administrative control and direction of the existing tuberculosis service.

The military metaphor of "the second front" has become familiar. In the war against tuberculosis, much attention has been given to the organisation of the adult front, and its results are plainly seen in the falling death-rates both in adults and children. The time has come to open a second front—a children's front, and the experience of the children in Papworth Village promises from it more decisive success in the campaign against tuberculous disease of the lungs in childhood.



In conclusion, the subject has been the peculiar features of tuberculous disease of the lungs in childhood, its prevalence, and the principles that must govern its better control in the future. These principles can be stated briefly; they are the discovery of the disease at its first stage of the primary complex, and its arrest at this stage. But control of the early phase of disease is not as good as prevention, and is more difficult in the child than in the adult. Prevention can only be attained by the discovery of a safe and efficient vaccine and by its widespread use.

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### DISCUSSION

*Professor Cameron* expressed his appreciation of Professor McNeil's paper and wished to make it clear that if he differed from him on certain points, it was entirely due to their different types of experience. In his opinion the statistics from sick children's hospitals showed a gloomier aspect of childhood tuberculosis than did those from sanatoria. The primary tuberculous infection in early childhood might advance rapidly, or it might become stabilised and heal. Those children in whom the disease advanced naturally went to the sick children's hospitals, while those in whom the disease became partly stabilised came to the sanatoria. The sick children's hospitals thus received the serious cases which were likely to die, while the sanatoria received cases the majority of which recovered. The child, even the very young child, was not without powers of resistance to tuberculosis. That was shown in the Lubeck disaster of 1927 when, of more than 250 children who received virulent doses of human tubercle bacilli instead of B.C.G., more than two-thirds survived.

Professor Cameron then quoted a series of figures dealing with different types of tuberculosis in early childhood treated in East Fortune Sanatorium. In twenty-three years 173 children of ages ranging up to 12 years were classed as having active primary infections of the lung. He confessed that all of these might not have been well-established cases, but the majority of them were, and, of the total, 5 children (aged 4, 6, 6, 8 and 10) developed fibro-caseous lung disease and died. Four (aged 3½, 4, 6 and 6½) died of miliary tuberculosis, and 2 (aged 2 and 4) died of miliary tuberculosis with terminal meningitis. One child (aged 8) died of tuberculous pericarditis. Many children had extensive active primary lesions and recovered after varying and often long periods of treatment. Twelve deaths in 173 cases was, he said, a small percentage. He then quoted detailed figures in children under 5 years of age of treatment of tuberculous neck glands and the lymphatic system generally, tuberculosis of spine, hip, knee, ankle, elbow, the bony system, the urinary system and abdomen, and finally he referred to a group, also under 5 years

of age, which had multiple disseminated lesions. The mortality throughout all of these groups was small, and even in the group with disseminated lesions the rate was below 25 per cent.

Professor Cameron then referred to a point raised by Professor McNeil when he stated that the group of Mantoux-positive children in the middle years of childhood who did not develop active tuberculosis probably was responsible for the lung tuberculosis which developed in adolescence and later life. He disputed the universal truth of this view from his own experience, and suggested that if a child had a primary infection which gave rise to symptoms and recovered it was very unlikely to develop tuberculous disease later. During twenty-three years in East Fortune Sanatorium probably not more than half a dozen children had come back in later life with lung tuberculous disease. In connection with the Mantoux test he stated that the sample surveys carried out in this country had only given scattered information about incidence of infection in different parts, and until the tuberculin test was carried out universally we would never have any information which would enable us to determine the interval which lay between the receipt of the infection and the development of lung tuberculosis. Tuberculin testing had become practically universal in Norway, and figures of great interest had already come from that country. He quoted a recent publication by Frostad of Oslo which dealt with 500 cases of primary infection developing in young adult life. An appreciable percentage of these patients developed adult lung tuberculosis, and the interesting point was that the disease developed in some cases within a year of the primary infection, and in all cases within five years. The interval between the primary infection and later lung disease might thus be very short. There was no doubt that in some cases it was long, and the Mantoux-positive child might quite well develop in later life a recrudescence of a secondary blood deposit in the lung or even of a partly healed primary focus which led to ulcerative lung disease. However, there was growing evidence that many cases of destructive lung tuberculosis in early adult life were the result of a recently acquired and progressive primary infection.

Referring to Professor McNeil's graph which showed the steady fall of tuberculosis since 1870 he questioned emphatically the part which anti-tuberculosis measures had played in the decreased mortality. He pointed out that the graph was already on the down-grade in 1870, twelve years before the tubercle bacillus was discovered and forty-two years before anti-tuberculosis measures of any kind were instituted. The truth was that wider forces were at work leading to an increasing immunity in a population which had long experience of the disease, and even since the introduction of anti-tuberculosis measures there had been no acceleration of the rate of mortality decrease. He did not decry these measures in any way, but rather pled for their improvement and intensification. They were likely to be of great help, but they were auxiliary to a decrease which was taking place from natural causes. We were, in fact, witnessing the fall of a long epidemic wave.

He then dealt with B.C.G. treatment to which Professor McNeil had referred, and pointed out that it had not been introduced in this country—not that the Ministry of Health considered it to be dangerous, but because the vaccine required careful control in its preparation with a view to maintaining its antigenicity. During the war years in Norway after 1941 a steady fall in these properties took place, and latterly the vaccine was failing to convert from Mantoux negative to Mantoux positive about 50 per cent. of those who

received it. The vaccine was undoubtedly a safe one to use, but until a constant antigenic power could be guaranteed it was wise not to circulate it.

Dealing with the question of contact infection he referred to a series of one thousand young adults suffering from lung tuberculosis whose family history had been investigated by Lloyd and Macpherson in the Brompton Hospital. A positive family history was found in 40 per cent., and in some series which he himself had investigated of patients in the Sanatorium he had found an even smaller figure. Thus, at least 60 per cent. of people develop lung tuberculosis from no known or obvious source, and although tuberculosis of childhood was often a focal disease, the destructive tuberculosis of later life in the majority of cases was not. The dissemination of tuberculous infection in the community was widespread. We already knew that from the few tuberculin surveys at our disposal, and it was being confirmed by mass radiography surveys.

*Professor Ellis* brought up the question of the social aspect of tuberculosis in childhood. This was important from the point of view of the general practitioner.

He referred to the dangers involved where the mother of a family is infected. Although placental transmission is rare, the danger to the newborn child is very great. He cited in particular one case of a normally healthy newborn child who, a few weeks after being taken home, developed tuberculous meningitis and died. Another case was where the father of a family was known to be infected but could not get a bed in a sanatorium. As a result, first one child contracted tuberculous meningitis and then a second child.

Professor Ellis was of the opinion that in addition to the two groups mentioned by the speaker, namely, the quickly developing tuberculosis and the rapidly stabilising type, there was a third, characterised by chronic ill-health, a condition which is frequently shown when the child is diagnosed radiologically as having a tuberculous lesion of the lung. It has then to be decided how long the child should be rested and what the future prognosis is likely to be.

In Professor Ellis's opinion there was no very simple answer to the problem. A child might be carefully investigated, stomach washings examined for T.B., pulse and respirations recorded at rest and after exercise, and the B.S.R. estimated, but none of these gives a complete and satisfactory answer. One sees cases where all these investigations are negative and yet the condition progresses radiologically. The only solution would appear to be frequent X-rays in individual cases and probably the wisest thing would be to err on the side of over-caution in returning the child to full activity.

*Professor Craig* referred to the possible dangers of contact met with in nurseries, nursery schools and other child communities. Instances, he said, had occurred of children developing the disease as a result of contact with a member of the staff of a nursery with active infection. It was, therefore, essential that all members of the staffs of such children's communities should be thoroughly examined before their appointment.

Evacuation, too, at the beginning of the war was responsible for the development of a certain number of cases. Arrangements in the early stages had to be made with such haste that there had been little or no time to investigate fully the environmental conditions under which the children were billeted.

With regard to B.C.G. treatment, Professor Craig commented upon the good results obtained by Dr Price in Dublin.

*Dr Traquair* referred to phlyctenular conjunctivitis, which occurs in the age group of one to five. Ophthalmologists regard this disease as a local indication of general tuberculous infection. These cases are much less common than they were some years ago and this fits in with the view that there is a decline in tuberculosis.

In its nature the condition may be regarded as a local reaction to tuberculin, an automatic Mantoux test as it were.

*Professor McNeil*, in reply, took note of the clinical material submitted by Professor Cameron, and of the less gloomy picture which it presented of pulmonary tuberculosis in childhood. His own account of the pathological processes was necessarily brief; nevertheless in a Children's Hospital, as in the Registrar-General's statistics, the dominating clinical type was tuberculous meningitis. Further, once active tuberculous disease attacked the lung tissues the course was usually progressive and fatal. In contrast, tuberculous pleural effusion in children had a good prognosis, and in 34 cases in his ward at the Children's Hospital there was immediate recovery in all.

The question of the relationship between the healed or arrested primary complex in the child and adolescent and adult tuberculosis was still unsettled, and there was evidence in support of the view that many cases of the disease in the adolescent represented the evolution of arrested primary lesions, the result of infection in childhood.

The President's remarks on phlyctenular conjunctivitis as a local tuberculous reaction were interesting, and it was significant that in those cases the cutaneous tuberculin test produced an unduly intense reaction.

## PULMONARY MYCOSIS \*

By T. GOW BROWN, M.D., F.R.C.P.E.

County Bacteriologist for Lanarkshire

MICROFUNGI are ubiquitous and are found as saprophytes or parasites on all forms of growth and decomposition.

The yeast fungus was first observed by Hook in 1677, but Ehrenberg's description of "Infusienthierchen" in 1828 may be considered the initial point in the investigation of the micro-organisms. Eight years later Cagnard-Latour and Schwann discovered the vegetable nature of yeast.

The lasting and active interest and the attendant controversies gave rise to varied opinions as to the most suitable and natural modes of classifying the thallophytes, but in 1886 Flügge departed from the botanical arrangement and, by adapting Frank's classification from Leunis' *Botany*, he divided the fungi into four main groups of which the first comprises the true fungi or mould fungi, the second the mycetoma, the third the yeast fungi or blastomycetes and the fourth the fission fungi or schizomycetes—the bacteria.

On the last group which has given rise to the entire sciences of bacteriology and immunology there is no need to dwell, for the impetus supplied by Pasteur and Lister to the study of bacterial infections completely swamped the interest in any other group.

Of the third group—the budding fungi—Flügge says: "Parasitic budding fungi have never as yet been observed in plants, and in animals they occur extremely rarely and then only as epiphytic parasites. The only known case of the latter kind is that of the fungus of thrush."

The etiological relationship between fungi and human disease had been established as early as 1839 by Schönlein in favus and by Robin and Lagenbeck in thrush, but the majority of fungi are non-pathogenic and considerable confusion cloaked their classification. In 1911, Vuillemin introduced further disorder into the classification of the blastomycetes, and Castellani, despite much good work, contributed not a little to the dissemination of the errors that existed.

In 1923 Berkhout showed considerable courage in attacking the problem and for the first time some semblance of definite advance in understanding was seen in her work on the genus "Candida." Diddens and Lodder have carried the good work further and the nomenclature of this group may be considered to be established.

The sixteen species described by Langeron and Guerra have been reduced to seven—that is species recovered from human sources—and of those Langeron believes that only one is pathogenic—*C. albicans*—although it has been claimed that *C. krusei* is also pathogenic.

\* Read at a meeting of the Medico-Chirurgical Society of Edinburgh on 4th December 1946.

As more workers enter the field of mycology we shall get a clearer conception of fungal diseases generally and of the infecting mycetes particularly, for there is an ever-increasing tendency to recognise fungi among the causes of disease.

Mycotic diseases of the lungs were considered to be very rare until comparatively recently, but are now universally recognised as being more prevalent than was suspected.

Most of the literature on the subject has originated in the United States of America and a review by the Flinns in 1931 disclosed that only eleven cases of pulmonary moniliasis had been reported in that country prior to that date. To-day reports from America, Australia, France, Italy, Scandinavia and other parts of Europe and South Africa show that fungal infections are widely distributed in tropical and temperate climates and the incidence is reported as high in the Southern United States.

Christie and Petersen, in discussing the significance of calcareous nodules in the chest, showed that if one can place any reliance on the tuberculin test as being of diagnostic value then a relatively large proportion of persons, particularly children, in the United States had radiological evidence of pulmonary disease that was not tuberculous.

Palmer had already reported his observations on the examination of 3105 student nurses by X-ray and tuberculin test. Of 294 nurses with pulmonary calcification only 21.4 per cent. reacted to tuberculin but the majority of the remainder reacted to histoplasmin.

Christie and Petersen carried this investigation further and added evidence supporting the view that calcareous lung deposits in tuberculin negative subjects may be associated with undiagnosed histoplasma infection.

There seems to be nothing specially characteristic in the X-ray shadows of the pulmonary nodules associated with positive histoplasmin skin reactions, but these nodules tend on the whole to be multiple and there are often several bilateral peripheral foci of calcification. In contrast the nodules found in persons positive only to tuberculin tend to be single and peripheral with usually only one lymphatic tract to the hilar nodes involved and there is less tendency to multiple deposits amongst the hilar nodes.

Emmons then proceeded to investigate the significance of the histoplasmin reaction. He showed common cross reactions with allergens from several fungi, and although his observations tended to invalidate the histoplasmin test as a specific reaction, they did not exclude the probability that calcified pulmonary nodules in tuberculin negative persons may be due to antigenically related fungi.

Perhaps some of the confusion that exists may be on account of the fact that there has been a failure to differentiate primary pulmonary mycosis from secondary pulmonary mycosis.

Goldstein and McDonald in discussing primary pulmonary coccidioidomycosis as occurring in California, New Mexico, Arizona and

Texas showed the disease to be quite different in character from the secondary disseminated mycosis that may show pulmonary manifestations following maybe initial cutaneous infection as is found in the commonly held conception of blastomycosis.

The coccidioidal granuloma was first described by Wernicke in 1892, but in 1937 Dickson recognised this description as that of secondary pulmonary invasion and not of an initial pulmonary disease.

Coccidioidal granuloma has a mortality rate of 50 to 60 per cent. It consists of intra- or extra-pulmonary lesions that become necrotic.

The incidence of the development of granuloma following acute primary pulmonary infection has not been established, but most workers agree that it is uncommon.

In primary infection the fungus does not seem to call forth much defensive reaction on the part of the host and there appears to be no cellular infiltration. Abscess formation may follow probably due to superadded secondary infection.

The symptoms depend on the degree, type and virulence of the infection. Mild cases give bronchitic changes, severe cases are associated with malaise, low-grade fever. The physical signs may be indistinguishable from tuberculosis, sarcoidosis, pneumoconiosis and many other lung infections.

In the series of cases reviewed by Goldstein and McDonald they were impressed by the mildness of the disease in one particular group and suggested varying virulence of the fungus *Coccidioides immitis*.

Thoracic pain aggravated by cough and deep inspiration was an early and prominent symptom.

Cough that was moderately productive was present in most cases, and hæmoptysis occurred in about 18 per cent., but it had no correlation with the severity of the disease.

Fever was a constant finding but the elevation of temperature was never excessive.

Physical signs varied from "harsh, rough breath sounds" to the classical signs of consolidation and pleural effusion.

The white blood count was of little diagnostic value but in some cases there was an eosinophilia.

The sedimentation rate was elevated while the disease was active, and that the return of the sedimentation test to normal was not always a sign of quiescence was shown by the Weltmann test giving a high band indicative of proliferative activity.

Tuberculin testing gave figures for reactors equal to that found in the general population and in no case was bacteriological evidence of tuberculosis found.

The coccidioidin skin test proved of great value in diagnosis for all patients gave positive results and one untoward reaction developed.

A positive serological test was considered diagnostic, but a negative test did not exclude the infection. Primary infection showed a high precipitin titre and a low complement fixation titre. In the

secondary granuloma complement fixation is high and the precipitin disappears.

X-rays showed hilar shadows enlarged on one or both sides with increased bronchovascular markings extending into the parenchyma of the involved regions. Most of those pictures showed gradual clearing in the ensuing weeks. A slight shadow may persist for several months. Cavity formation occurred in a few cases and initial infection was manifested by pleural effusion in others.

Those workers claim that the recognition of pulmonary mycosis is not difficult if the disease is included in the differential diagnosis. This is especially true if the patient lives in an endemic area. Also one should always consider this condition if the patient, suspected of having pulmonary tuberculosis, has a persistently negative sputum.

The symptomatic similarity of pulmonary mycosis and pulmonary tuberculosis is so close that the parallelism between the two diseases renders it imperative to enlist laboratory aid to arrive at a definite differentiation, at least until such time as a better understanding of pulmonary mycosis is reached.

This is a matter of considerable importance for in endemic areas primary pulmonary mycosis has been shown to have a high morbidity rate and a low mortality rate, and infection does not take place from case to case but by the inhalation of spores present in dust and sand.

From what I have said it is apparent that this new interest in medical mycology has been going on for twenty-five years in the United States and for a considerable period in South America, France and Italy.

Recently the awakening interest has spread to the British Empire and to other countries, but the study of mycology in this country has been more or less restricted to skin diseases. A few cases of pulmonary mycosis have been described, but undoubtedly the manifestations in some instances have been allergic reactions to aspergillus, the pathogenic nature of the alleged infecting fungus has not always been established and the guarded warning of Castellani that a fungus isolated from sputum may be (a) a contaminant, (b) a saprophyte living on dead material in bronchiectatic cavities, or (c) if pathogenic those properties must be established by animal experiment, has created a feeling of frustration in anyone wishing to pursue investigations along this path.

Although the interest in mycology may not have attracted much attention the increased intensity of the anti-tuberculosis campaign with its modern mass-production methods has enabled me to observe something I should have seen many years ago. I had seen occasionally what I now see persistently, but it was only the realisation that a ridiculously large number of persons were coming under observation as probable cases of pulmonary tuberculosis that made me look for an explanation.

For many years I had seen specimens of sputum that looked like



watered milk. I proceeded to investigate those sputa to discover the nature of the infection and to establish data that would make its recognition as easy as possible and to define its essential features. The sputum from the same patient varies little in character over periods of months.

An occasional specimen may be of a mixed character due to co-existent pyogenic infection, but generally the sputum is fluid and of a dead-white to greyish-white colour. On standing, a white flocculent deposit separates from a slightly opalescent supernatant fluid. The important constituent is the white flocculent particle.

Microscopic examination reveals this deposit to be composed of epithelial cells and macrophages with either very few or, in most instances, an entire absence of polymorphonuclear or lymphocytic cells. Spores of varying sizes may be demonstrated but this is not a constant finding.

The macroscopic and microscopic appearance is striking and typical.

It is unlike any reactive result of the usual bacterial infections and the underlying process would appear to be proliferative and not inflammatory.

The appearance of yeast-like bodies in some of those sputa led me to investigate the possibility of a mycotic infection and I was able to isolate *Candida albicans* from specimens from 467 persons in the course of one year.

The next step was to prove the pathogenicity of the fungus. Using a suspension of a pure culture grown on Sabouraud's medium I inoculated rabbits intravenously and my first half-dozen animals died within a week of uræmia. There was a miliary granulomatous condition that was most marked in the kidneys and, as was to be expected in a blood stream infection, the cortical region showed greatest involvement just as is seen in tuberculosis of the kidney.

I next tried intradermal inoculation and the animals survived for a little over a fortnight and developed a rather more widespread miliary granuloma, but on the whole the appearances were similar to those in the previous experiments.

So far the suspensions of *Candida* had been haphazard so I now proceeded to inoculate estimated numbers of spores to find the effect.

As few as 100 million were as dramatic in result as larger quantities. Death from uræmia took place as quickly from a devastating infection of the kidney.

Having established pathogenicity I was able to discover the clinical condition of many of the patients.

Of the similarity of the clinical manifestations of pulmonary mycosis and pulmonary tuberculosis there can be no doubt, for although 59 of the 467 persons investigated had tuberculous as well as mycotic infections specimens from all of the remaining 408 persons were submitted to cultural and biological examination for tuberculosis

with negative result. All were suspected as having tuberculosis either on clinical or radiological grounds and many had been admitted to sanatoria or were attending tuberculosis dispensaries.

A selection may give some indication of the extent to which mycotic disease may simulate the more serious infection.

1. Mrs G. was diagnosed in 1939 as advanced pulmonary tuberculosis with cavitation. An eminent phthisiologist pronounced the outlook as hopeless and advised sanatorium treatment and artificial pneumothorax. The latter advice was not accepted and six years later the patient's general condition was not depressed in any way. As she had a persistently negative sputum she was allowed home and has been quite fit to carry on normal household duties throughout the war years. Her sputum had the characteristic appearance of mycosis and *Candida albicans* was isolated repeatedly.

2. R. B. (18) was turned down by a Medical Board and referred to his home local authority as pulmonary tuberculosis. His sputum was persistently negative for *B. tuberculosis* but was copious and of the typical mycosis type; *Candida albicans* was isolated on repeated examination over a period of eight months.

3. C. C. (42) had had a hæmoptysis and was attending a tuberculosis dispensary. Her sputum was persistently negative for *B. tuberculosis* but had the characteristic appearance of mycosis; *Candida albicans* was isolated on repeated examination over several months.

4. A. A. (21), a member of W.R.N.S., had a pulmonary complaint diagnosed as basal pneumonia. This did not respond to treatment but left persistent dullness and cough. The sputum was typical of a pure mycotic infection; *Candida albicans* was isolated.

5. J. McC. (5), a small boy, had a persistent cough with sputum and a complaint of chestiness. The sputum had the characteristic mycotic appearance and *Candida albicans* was isolated.

6. W. S. had a history of febrile attacks for nine months with recurring "colds" and cough. His sputum had the characteristic appearance of mycosis; *Candida albicans* was isolated.

7. Mrs M. G. was diagnosed as suffering from pneumonia which did not respond satisfactorily to penicillin. Her sputum was characteristic of mycosis and *Candida albicans* was isolated.

8. J. L. was admitted to hospital suffering from pneumonia and, while the clinician was satisfied that the classical signs were present and that radiological examination showed extensive consolidation, the patient's general condition was not consistent as he felt and looked "perfectly well." The sputum was typically mycotic and *Candida albicans* was isolated repeatedly.

A further interesting analogy with pulmonary tuberculosis is that several members of a family have suffered from this infection.

A mother, son and daughter were under observation at the same time for tuberculosis; all had negative sputa for *B. tuberculosis* but all were typical mycosis. *Candida albicans* was isolated repeatedly from each patient.

Two sisters were in a sanatorium without confirmatory bacteriological evidence of tuberculosis while their brother at home was under observation. All three had typical mycotic sputa from which *Candida*

*albicans* was isolated repeatedly and all attempts to prove a tuberculous basis for their illnesses proved sterile.

From these few examples it is evident that clinical diagnostic difficulties make the differentiation of mycosis and tuberculosis a matter of extreme finesse unless careful scrutiny of the sputum is carried out.

As a student I was impressed more by the insistence of my teachers on using the powers of observation and of the importance of examining carefully such unpleasant substances as might be derived from the patient under scrutiny. The interest to be found soon overcame the civilised disgust that surrounded natural functions and much value could accrue from a use of the senses.

To-day it seems that the clinician is above looking at sputum for it is merely submitted to the laboratory in the hope that a spot diagnosis may be confirmed.

Mycotic disease should always be considered in the differential diagnosis of any pulmonary complaint and particularly in patients suspected of having pulmonary tuberculosis with a persistently negative sputum.

The character of the sputum should be noted carefully as the naked-eye appearance of the white flecks is characteristic and can be recognised easily even in a mixed infection.

From my observation throughout the past few years it would seem that mycotic infection of the lungs is much more prevalent than is suspected, but I hope that further work may be done on this apparently not very serious clinical condition, as its primary form can upset the national economy if it is erroneously diagnosed as pulmonary tuberculosis.

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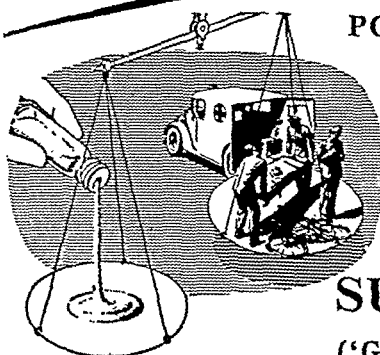
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## DISCUSSION

*Professor Cameron* thanked Dr Brown for an interesting talk about a subject which had perplexed a great many physicians whose interest lay in diseases of the chest. Many patients were suspected to have fungus infections of the lungs and X-ray examination often suggested the presence of that condition. More often than not the condition was never proved on the laboratory side, and the diagnosis went by default. He referred to the large number of cases (467) seen by Dr Brown and wondered whether these fungus infections were localised to different areas of the country. He said that he had all his life made a point of inspecting sputa, and not only inspected the sputum of every patient under his care but examined it at least weekly and very often daily. In all these thousands of examinations he did not remember seeing the type of sputum which Dr Brown demonstrated. If it had occurred frequently it would have been noticed, and that was why he wondered if the condition was common in Lanarkshire and rare in the East of Scotland.

He then referred to the type of fungus infection occurring in Cumberland about which Fawcett and Munro Campbell had written. These infections were of a different type from monilia, and were of penicillium, aspergillus, mucor and allied species. Marett, many years ago, had described a high incidence of monilia lung infection in Jersey, and had attributed it to milk infection. There was a good deal of controversy at the time about Marett's findings, and many people questioned whether the monilia were actually disease producers or saprophytes. The fact, however, remained that its presence in sputum seemed to be common in Jersey, and the type of infection Munro Campbell and Fawcett described seemed to be common in Cumberland.

He referred to the growing U.S.A. literature on fungus infections, and agreed with Dr Gow Brown that these infections were evidently much more frequent in America than they were in this country. Coccidioidomycosis did not occur in Great Britain, and blastomycosis and torulosis were relatively infrequent. There was little doubt that cases of fungus infection that were not treated could develop lung changes very like those of long-standing tuberculosis. It seemed strange to him, however, that the condition should be so common in Lanarkshire while he, on careful examination of every patient from every point of view in a large sanatorium over a period of twenty-five years, had never had a confirmed case. He agreed entirely with Dr Gow Brown that these cases could never be confirmed unless they were investigated by a bacteriologist with mycological experience.

*Dr Kininmonth* said that radiologically they had often found patients showing multiple scattered calcifications which suggested a fairly widespread infection, but frequently in these cases there was little or no history of previous illness suggesting the onset of any infection, which was surprising. He wondered if many of these cases were due to a mycotic infection.

*Dr Peterkin* was interested to know if this infection occurs in definite types of individuals. In women liable to yeast infections of the skin flexures, there is often a hyperchlorhydria and a hypochromic anaemia.

Dr Peterkin noted that Dr Brown had made no reference to treatment other than the use of iodine, which he himself had found of little value. Castellani may have confused the issue with regard to the classification of mycosis, but Dr Peterkin had found his paint of great value in skin mycosis.

*Dr Douglas Guthrie* said that it would be interesting to know to what extent wild animals were subject to mycotic infection. Several years ago it was prevalent among kangaroos in the Edinburgh Zoological Park and caused the deaths of several consecutive series of those animals shortly after their arrival from Australia. Mycosis was also common in penguins. If the disease is found in wild animals in captivity it may also occur in domestic animals, and may be transmissible from them to man. This aspect of the problem appeared to demand closer investigation.

*Dr Gow Brown*, in reply, said that he knew very little about mycotic disease in animals. Aspergillosis is very common in birds, and that is one of the possible sources of pulmonary mycosis in humans. Aspergillosis has been found in several farm workers, but whether they were cases of true mycosis or an allergy, it was difficult to say. Fawcett reported a number of cases of possible aspergillosis in the chest, but some investigators recorded histories that were rather peculiar because the patients had had chest complaints which disappeared when the patient was removed from his occupation, only to return on resumption of work. This would suggest an allergy rather than a true infection. Dr Brown was of the opinion that until it was decided what type of patient was sensitive to mycotic disease, and what particular type of fungus produced it, no real progress could be made.

# NON-SPECIFIC URETHRITIS OF VIRUS ÆTIOLOGY

By P. N. MEENAN, M.D., D.C.P.

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IN recent years considerable interest has been shown in non-gonococcal infection of the genito-urinary tract. Among the various causes of so-called non-specific urethritis, viruses must be considered. This article reviews the evidence for a virus ætiology of a proportion of these cases, which has become more convincing as a result of recent work.

The only virus group that has so far definitely been incriminated is that characterised by the presence of large basophilic inclusion bodies. The viruses of this group include trachoma, inclusion conjunctivitis and the lymphogranuloma-psittacosis-pneumonitis subgroup. The inclusions, as described in trachoma, for example (Halberstadter and von Prowazek, 1907) undergo a developmental cycle; minor morphological differences can be observed among the members of the group.

Only two members of this group of viruses are commonly recognised as causing genital lesions. Thus it is well known that lymphogranuloma inguinale may present as a localised ulcer or nodule or as a non-gonococcal urethritis before the appearance of the bubo. Basophilic inclusions can be found in urethral scrapings, and the Frei intradermal skin-sensitivity test becomes positive; in convalescence complement fixing antibodies develop in the blood; the virus can be readily transmitted to mice, guinea-pigs and the yolk sac of the fertile egg (see van Rooyen and Rhodes, 1940). Owing to the close antigenic similarity between the viruses of the lymphogranuloma-psittacosis-pneumonitis group neither the Frei nor the complement fixation test are specific for infection with the virus of lymphogranuloma, and positive reactions occur also in psittacosis and pneumonitis (see *e.g.* Rake, Eaton and Shaffer, 1941).

The other virus that definitely causes genital lesions is that of virus ophthalmia (inclusion conjunctivitis, "swimming bath" conjunctivitis or inclusion blennorrhœa). Infection with this virus, as the name suggests, is usually recognised in the conjunctiva by the demonstration of basophilic inclusions in epithelial cells. Examination of urethral and cervical scrapings from parents of children suffering from the neonatal form of the disease has shown the presence of basophilic inclusions (Halberstadter and von Prowazek, 1909, 1910; Heymann, 1910; Thygeson, 1934; Thygeson and Mengert, 1936; Thygeson and Stone, 1942; Sorsby, Hoffa and Young, 1944).

There seems little doubt that this virus is an occasional cause of urethritis and cervicitis. Thygeson and Stone, by means of direct



microscopic examination of smears and baboon inoculation, were able to demonstrate the virus in 13 out of 38 mothers. In a series of 184 non-pregnant women investigated for various gynaecological complaints they demonstrated the virus in 10 cases. In no case did they demonstrate inclusions in material from the female urethra, but the virus was recovered by baboon inoculation in 8 of 100 cases of male urethritis, in 6 of which it was associated with typical gonorrhœal infection. They conclude that the "reservoir" of the virus is a mild genito-urinary disease which is probably transmitted venereally; a low-grade non-gonococcal urethritis is found in the male, and sub-clinical cervicitis, limited to the region of transitional epithelium just within the external os, in the female.

Evidence has thus been accumulating to suggest that agents of the trachoma-inclusion conjunctivitis-lymphogranuloma group cause a proportion of cases of non-specific urethritis. A most interesting example of this condition is Waelsch's urethritis, which Harrison and Worms (1939) describe as pursuing a chronic course with mild symptoms, rather scanty glairy or muco-purulent discharge, together with characteristic urethroscopic appearances. It was first described by Waelsch in 1901, but many writers, including Waelsch himself (1916), either do not mention the urethroscopic findings, first described by Glingar (1914), or do not regard them as necessary for diagnosis. This confusion renders it difficult in dealing with the literature to come to any precise conclusion as to whether a given author was dealing simply with a non-gonococcal urethritis or one which fulfils the criteria of Harrison and Worms. Its interest lies in the fact that inclusions have been described in non-gonococcal urethritis, including cases of Waelsch's urethritis, by Halberstadter and von Prowazek (1910), Lindner (1910), Fritsch, Hofstatter and Lindner (1910), Siebert (1910), Scherber (1935), Thygeson and Mengert (1936) and Thygeson and Stone (1942).

In spite of their clinical disparity, Waelsch's urethritis, lymphogranuloma and inclusion conjunctivitis are closely linked. As has been shown, the viruses of lymphogranuloma inguinale and inclusion blennorrhœa belong to the same group, and there is evidence, reviewed by Harrison and Worms, to link up Waelsch's urethritis with lymphogranuloma. Thus the observations of Frei, Weise and Klestadt (1932) and Bezecky (1934) showed that a positive Frei reaction could be obtained in cases of lymphogranuloma by the intracutaneous injection of urethral discharge from patients with Waelsch's urethritis. Of these cases it should be noticed that the earlier, although diagnosed as Waelsch's urethritis, did not fulfil the criteria laid down by Harrison and Worms, but the case described by Bezecky did. He prepared the antigen from the urethral exudate in the same fashion as the antigen for the Frei test, and inoculated the test preparation and known Frei antigen in 5 cases of lymphogranuloma inguinale. In four of these positive reactions to both antigens were obtained, the

fifth giving a weakly positive Frei test only. Twelve control cases were negative to both preparations. Similar results have been reported by Curth (1931), Kalz (1933), Polak (1933) and Gray (1936). Conversely, positive skin reactions to Frei antigen in patients with Waelsch's urethritis were reported by Bezechny (1934), Fahlbusch and Zierl (1937) and Ross (1939). Bizzozero and Midana (1938), as a result of obtaining skin reactions with Frei antigen in 15 out of 18 cases of Waelsch's urethritis, concluded that the majority of these cases are in fact lymphogranuloma. As against this, urethral secretion from cases of Waelsch's urethritis does not produce meningo-encephalitis in mice, although lymphogranulomatous material will do so (Ross, 1939). Further, as mentioned above, the Frei test has lost much of its value as a specific test as a result of recent experimental work on the antigenic structure of this group of viruses.

True Waelsch's urethritis responds rapidly to treatment with sulphonamides (Harrison and Worms, 1939; Ross, 1939); both lymphogranuloma (Findlay, 1940) and inclusion blennorrhœa (Thygeson, 1941) are also susceptible. The theoretical basis for this sensitivity cannot yet be explained (Meenan, 1945; Andrewes and King, 1946).

It would seem, therefore, that there is a well-defined group of conditions characterised by urethritis or cervicitis, which, in spite of seeming clinical disparity, are in fact closely linked. The incidence of these cases is at present unknown and more information is needed which can only be made available by the fuller examination of all cases of non-specific urethritis.

### SUMMARY

The evidence for a virus ætiology of a proportion of cases of non-gonococcal urethritis is reviewed in the light of recent experimental work on the lymphogranuloma-psittacosis-pneumonitis group of viruses.

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## BACTERIÆMIA, A FACTOR OF PROGNOSIS IN PNEUMONIA

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BACTERIÆMIA occurs when the organisms producing the pneumonia either penetrate the lung alveoli and invade the blood stream, or alternatively, gain admission to the circulation directly through the lymphatics and venules of the lung stroma. The presence of bacteriæmia cannot be surmised from the extent of lung involved nor can it be predicted from the character of the disease either at the onset or later in the course of the illness; the extent, character and degree of blood infection may be determined only by blood culture.

In pneumococcal pneumonia the demonstrable presence of the invading organism in the blood stream of the patient is a factor which has received increasing recognition as influencing the prognosis of the illness at an early stage. Thus, in the years immediately antedating the use of the sulphonamides in the treatment of pneumonia, Finland and Tilghman<sup>1</sup> in a series of 170 patients showed a bacteriæmic incidence of 40·8 per cent. with a corresponding fatality rate of 82 per cent.; Rosenbluth and Bloch<sup>2</sup> found positive blood cultures in 34·5 per cent. of patients, 70 per cent. of whom died; while in 1929 Bullowa,<sup>3</sup> basing his conclusions on observations of 937 patients, 40 per cent. of whom had positive blood cultures, stated that, among bacteriæmic patients suffering from lobar pneumonia, a fatality rate of up to 70 per cent. was to be expected. Cruikshank<sup>4</sup> had a bacteriæmic incidence of 25·5 per cent. among 329 patients, with a fatality rate of 40·5 per cent. After the introduction of sulphonamide therapy in 1938 the position altered, but only in degree, for Don *et al.*<sup>5</sup> in a series of 119 patients showed that 25 per cent. died when there was bacteriæmia; Alstad<sup>6</sup> in a series of 160 patients found positive blood cultures in 20·2 per cent., and a corresponding fatality rate of 41·2 per cent.; Price and Myers<sup>7</sup> had a bacteriæmic death-rate of 48·5 per cent. in a series of 115 patients; Anderson and Cairns,<sup>8</sup> and Macartney *et al.*<sup>9</sup> found similar results. Furthermore, in a large series extending from 1938 to 1942, in which the present author collaborated (Aitchison *et al.*<sup>10</sup>), out of 1356 patients 277 or 20·5 per cent. had positive blood cultures, and of these 91 or 32·8 per cent. died, whereas the fatality rate among the non-bacteriæmic was only 6·5 per cent. This series represented the experience of the disease in Glasgow over five consecutive years, all the patients comprising it receiving sulphonamide therapy. Already there are some reports of lobar pneumonia treated by penicillin, but unfortunately few mention the incidence of bacteriæmia among the patients treated. Such reports

as give this information, however, indicate that in the presence of a positive blood culture the disease is still attended by a much greater fatality rate even although lower rates of mortality tend to occur than with other methods of treatment. For example, Meads, Harris and Finland<sup>11</sup> found bacteraemia to be present in 29 out of 54 patients, 10 of whom died, 8 having positive blood cultures. Tillet *et al.*<sup>12</sup> experienced a fatality rate of 14.3 per cent. in the bacteraemic as compared with 3.3 per cent. in the non-bacteraemic, while Anderson and Ferguson<sup>13</sup> had 4 deaths among 12 patients whose blood cultures were positive, contrasting with 3 deaths among 51 non-bacteraemic cases.

It would seem, therefore, that when the causal organism is present in the blood, and is demonstrable there by the usual methods of blood culture, a different prognosis is to be formulated than that for those patients who are non-bacteraemic, even although they have administered to them drugs of the sulphonamide series or even penicillin. It may be useful to examine in greater detail the data collected from a series of 160 patients suffering from lobar pneumonia and treated by sulphonamide in order to ascertain, if possible, the various other criteria which, considered in relation to bacteraemia, aid in the formation of an accurate prognosis. The sulphonamide used was sulphapyridine, and although this drug has been replaced by sulphadiazine, sulphathiazole, or sulphamerazine in the treatment of pneumonia the results may be of value as an indication that in similar investigations with sulphonamides, and even with penicillin or streptomycin, the same factors may operate.

Of the 160 patients to whom reference has just been made, 34 or 20.2 per cent. had positive blood cultures, and the fatality rate among them was 41.2 per cent. as compared with 7.1 per cent. in the non-bacteraemic, and 14.4 per cent. in the whole series. All the patients were examined daily as to their leucocyte and differential counts, and the blood concentration of sulphonamide maintained by them was estimated each day while treatment was continued. The causal organism in each case was identified and typed both directly and after passage through a mouse. The extent of lung involvement, as determined by clinical examination, was confirmed by radiological methods. Fluid intake was carefully maintained at not less than 5-6 pints per diem.

Reference to Table I, *a* to *d*, will show the influence of certain factors on mortality, particularly among the bacteraemic patients. The fatality rate varies with the age of the patient, increasing as the age advances, thus (grouping the patients as under or over forty-five years to minimise error, the number in each group being small) in the bacteraemic, 4 or 23.5 per cent. under forty-five years died, and 10 or 58.8 per cent. over forty-five years succumbed, whereas the corresponding figures in the non-bacteraemic are 6 or 6.9 per cent. and 3 or 8.5 per cent. respectively. Similarly, an increase in the

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amount of lung tissue involved by the disease is associated with an  
increasing fatality rate, for in the non-bacteriæmic, if less than two

TABLE I  
(a) Influence of Age on Fatality Rate

Age in Years.	Bacteriæmic.			Non-bacteriæmic.		
	Total.	Died.	Fatality Rate (per cent.).	Total.	Died.	Fatality Rate (per cent.).
15-25	4	...	0.0	31	...	0.0
25-45	13	4	30.7	60	6	10.0
45-65	16	9	56.2	32	2	6.3
65-75	1	1	...	3	1	...
15-45	17	4	23.5	91	6	6.9
45-75	17	10	58.8	35	3	8.5

(b) Influence of Type of Pneumococcus on Fatality Rate

Type of Organism.	Bacteriæmic.			Non-bacteriæmic.		
	Total.	Died.	Fatality Rate (per cent.).	Total.	Died.	Fatality Rate (per cent.).
I.	5	3	60.0	20	0	0.0
II.	15	3	20.0	43	2	4.7
III.	5	4	80.0	13	2	15.4
Group IV	9	4	44.4	50	5	10.0

(c) Influence of Degree of Lung involved on Fatality Rate

No. of Lobes involved.	Bacteriæmic.			Non-bacteriæmic.		
	Total.	Died.	Fatality Rate (per cent.).	Total.	Died.	Fatality Rate (per cent.).
1	10	1	10.0	69	3	4.4
2	17	7	41.2	48	5	10.4
3	6	5	83.3	9	1	11.1
3+	1	1	...	...	...	...
Under 2	10	1	10.0	69	3	4.4
Over 2	24	13	54.2	57	6	10.6

(d) Influence of Blood Level of Sulphapyridine on Fatality Rate

Blood Level in mgms. /100 c.c.	Bacteriæmic.			Non-bacteriæmic.		
	Total.	Died.	Fatality Rate (per cent.).	Total.	Died.	Fatality Rate (per cent.).
3-5	4	3	75.0	21	4	19.1
5-7	17	8	47.1	62	4	6.5
7-9	11	3	27.3	33	0	0.0
9+	2	...	0.0	10	1	10.0
3-7	21	11	54.4	83	8	9.6
7+	13	3	23.0	43	1	2.3

lobes are consolidated the fatality rate is 4.4 per cent., while if more  
than two lobes are affected the mortality is 10.6 per cent. The



corresponding rates among those who had a positive blood culture are 10.0 and 54.2 per cent. respectively. It will be seen that the type of pneumococcus producing the illness will affect the fatality rate, and that the fatality rate respective of the type of organism is always much greater if bacteriæmia be present; thus in the non-bacteriæmic the fatality rate in type I, II, II, and group IV pneumonias is 0.0, 4.7, 15.4, and 10.0 per cent. respectively, whereas the corresponding figures in the same order in the bacteriæmic are 60.0, 20.0, 80.0, and 44.4 per cent. Finally, Table I (*d*) presents the average blood concentration

TABLE II

(a) *Leucocyte Response in Bacteriæmic and Non-bacteriæmic Patients*

Day of Treatment.	Average Leucocyte Count per c.mm.	
	Bacteriæmic.	Non-bacteriæmic.
1	17,200	15,100
2	15,900	14,200
3	14,400	12,700
4	12,600	11,200
5	12,600	10,200
6	12,000	9,200
7	11,600	9,000
8	8,400	9,200

(b) *Leucocyte Counts in Bacteriæmic Patients by Recovery and Death*

Day of Treatment.	Recoveries.		Deaths.	
	Under 15,000/c.mm.	Over 15,000/c.mm.	Under 15,000/c.mm.	Over 15,000/c.mm.
1	2	18 (90.0)	9	5 (35.7)
2	4	16 (80.0)	7	4 (36.4)
3	12	8 (40.0)	7	3 (30.0)
4	12	8 (40.0)	7	1 (12.5)
5	13	7 (35.0)	7	0 ...
6	15	3 (16.7)	6	1 (14.5)
7	12	4 (25.0)	4	0 ...
8	9	0 ...	1	0 ...

(Figures in brackets are percentages)

of sulphapyridine maintained by these patients during treatment, and a remarkable relationship is evident between the blood level of the drug and the fatality rate, for at higher blood concentrations the death-rate is lower than when the concentration is small. This relationship is present respective or irrespective of the presence of a positive blood culture. The fatality rate decreases from 52.4 per cent. in bacteriæmic patients with blood levels less than 7 mgms. per 100 c.c. to 23.0 per cent. when the blood level is over 7 mgms. per 100 c.c. The corresponding percentages in the non-bacteriæmic are 9.6 and 2.3 respectively.

The leucocyte response of the patients is shown in Table II, which also records the number and percentage of the bacteriæmic who

recovered or died, subdivided according as their daily leucocyte count was above or below 15,000 cells per c.mm.

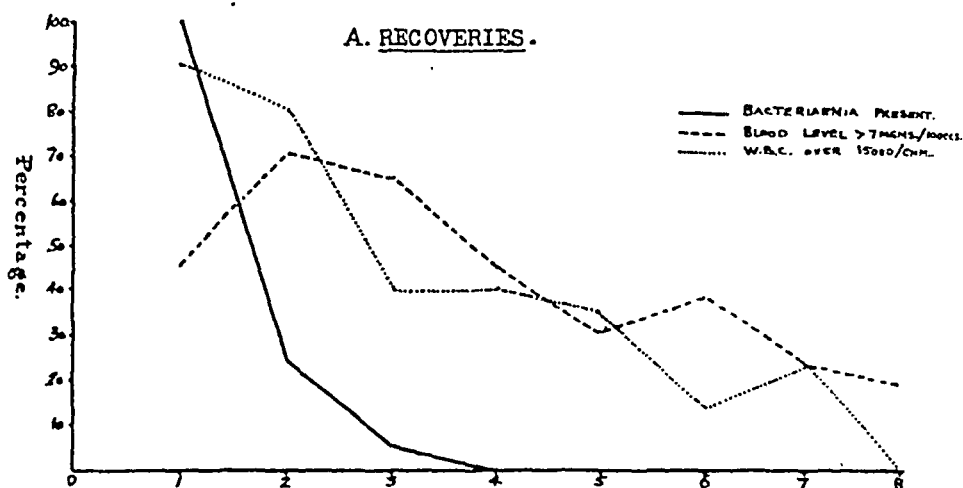
As these patients all received sulphonamide during this period, it is interesting to note that the use of the drug does not affect in any great measure the leucocyte count. It will be seen that there is a difference between the average daily leucocyte count in the bacteriæmic and non-bacteriæmic, but that this difference is one of degree and not of trend. A considerable difference in trend of the daily counts does exist when the bacteriæmic are subdivided in respect of the final outcome of the illness. Of the recoveries, 90 per cent. had initial counts of over 15,000 cells per c.mm., while only 35·7 per cent. of the deaths had initial counts of this degree; and while a considerable percentage of the recoveries maintain such high counts as the illness progresses, the percentage of deaths with high white cell counts steadily diminishes. It is of interest to consider these results in relation to the duration of the bacteriæmia and to the blood concentration of the drug from day to day, and this may be done by reference to the accompanying graphs.

These graphs show the percentage number of patients who, having positive blood cultures, lived or died, and who maintained a blood level of drug greater than 7 mgms. per 100 c.c., and had a daily leucocyte count greater than 15,000 cells per c.mm. Those who recovered show a greater percentage with a high blood level and leucocytosis than did those who died, and the number among them with organisms persisting in the blood rapidly diminishes. Patients who died are distinctive in having a much smaller number who maintained high concentrations or who had a high leucocyte response, while among them bacteriæmia persisted over a much longer period. This may indicate that when the body defences (as measured by the leucocyte response, and by the continued presence of organisms in the blood stream) are impaired to the extent of being ineffective, a low blood level of the drug results from defective absorption and thus its beneficial effects are minimised.

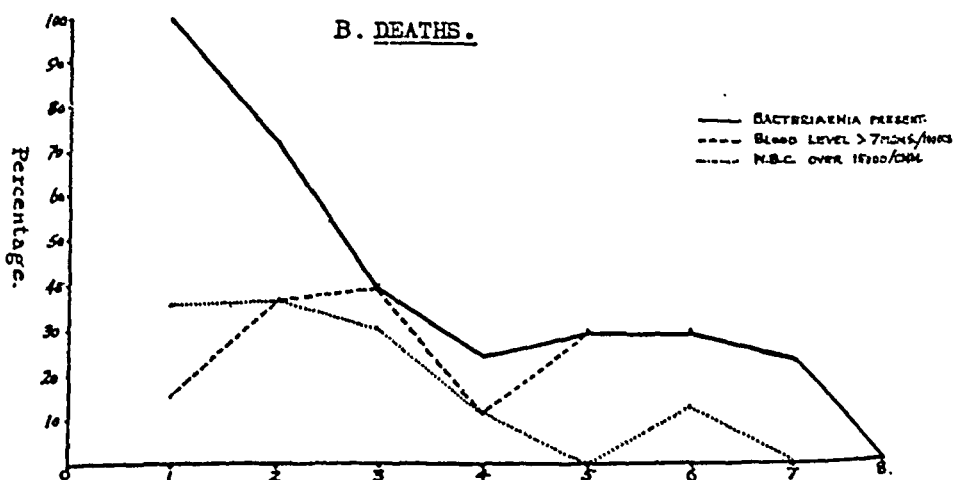
The value of the differential leucocyte count in determining the course and outcome of lobar pneumonia is well known, and is of particular importance when sulphonamides are used in treatment, since by this means any tendency to agranulocytosis may be recognised at an early stage. Variations in the differential count in bacteriæmic recoveries and deaths are set out in Tables III and IV.

There emerges that among the recoveries a good leucocytosis with high granulocytosis and a moderate number of young forms (*i.e.* a moderate "shift to the left") in the earlier days of treatment rapidly gives place to a more normal white cell count with a lower granulocytosis and the disappearance of immature forms, but with an increasing number of lymphocytes and monocytes. Among the deaths a rather different picture is seen, for a lower initial count is accompanied by only a moderate granulocytosis with the more noticeable presence of immature forms. This picture changes as treatment advances, and

*Percentage Distribution of Recoveries and Deaths, with respect to Bacteraemia High Leucocyte Count, and Blood Concentration of Sulphapyridine over 7 mgms. per 100 c.c.*



	Day of Treatment.							
	1	2	3	4	5	6	7	8
Bacteraemia present . . . . .	100.0	25.0	5.0	...	...	...	...	...
W.B.C. over 15,000/c.mm. . . . .	90.0	80.0	40.0	40.0	35.0	16.7	25.0	...
Blood level > 7 mgms. per cent. . . . .	45.0	70.0	65.0	45.0	30.0	38.9	25.0	22.2
Number of patients . . . . .	20	20	20	20	20	18	16	9



	Day of Treatment.							
	1	2	3	4	5	6	7	8
Bacteraemia present . . . . .	100.0	72.7	40.0	25.0	28.5	28.5	25.0	...
W.B.C. over 15,000/c.mm. . . . .	35.7	36.4	30.0	12.5	0.0	14.3	0.0	...
Blood level > 7 mgms. per cent. . . . .	14.5	36.4	40.0	12.5	28.5	28.5	25.0	...
Number of patients . . . . .	14	11	10	8	7	7	4	1

particularly noticeable is the tendency to an increasing proportion of immature cells, or "shift to the left," without the appearance of large numbers of lymphocytes and monocytes. It is evident, therefore, that these results conform to the principles of leucocyte change in pyogenic infections, as propounded by Schilling,<sup>14</sup> and supported by Whitby and Britton,<sup>15</sup> namely, that when the response to infection is favourable, a good leucocytosis is usually accompanied by a moderate "shift to the left," and that as healing proceeds this disappears, while lymphocytes and monocytes appear in increasing numbers; but when the infection

TABLE III

*Differential Leucocyte Count in Bacteriæmic Recoveries*  
(Actual Number per c.mm.)

Day of Treatment.	Granulocytes.	Polymorpho-nuclear L.	Metamyelo-cytes.	Myelocytes.	Monocytes.	Lympho-cytes.
1	16,900	12,490	3830	600	500	1550
2	14,850	11,060	3300	490	630	1820
3	12,480	9,770	2370	340	580	1990
4	10,060	8,030	1590	440	650	2020
5	10,590	8,200	1460	930	920	2640
6	9,220	7,680	1310	230	830	2290
7	7,430	6,700	600	130	850	2630

TABLE IV

*Differential Leucocyte Count in Bacteriæmic Deaths*  
(Actual Number per c.mm.)

Day of Treatment.	Granulocytes.	Polymorpho-nuclear L.	Metamyelo-cytes.	Myelocytes.	Monocytes.	Lympho-cytes.
1	11,960	9300	2200	460	270	1350
2	13,350	8820	2100	430	330	1270
3	10,020	7500	2130	390	220	1300
4	10,050	7500	1740	810	350	1010
5	7,510	5600	1300	610	350	1330
6	8,670	6400	1620	650	350	1500
7	7,550	5420	1610	520	420	1060

is fatal a low total leucocyte count is often accompanied by an increasing number of immature cells.

An important aspect of bacteriæmia is the relationship of the duration of a positive blood culture to the outcome of the illness, and to the blood concentration of sulphonamide maintained. Table V (a) sets out the duration of bacteriæmia in those who recovered and in those who died, and shows the fatality rates found when a positive blood culture persisted for one or more days. It is evident that in patients who are going to recover, the bacteriæmia was controlled in all but one case before the third day of treatment, whereas 4 out of the 14 deaths had positive cultures after the second day of treatment. The fatality rate increases with the duration of bacteriæmia.

When the duration of bacteraemia is correlated with the blood concentration as in Table V (*b*), it is seen that not only did all patients in whom a positive blood culture persisted for more than two days have blood concentrations less than 7 mgms. per 100 c.c., but that when bacteraemia persisted for two or more days, 7 out of 9 patients died when the blood level was low, compared with 1 death in 4 who had blood concentrations greater than 7 mgms. per 100 c.c.

TABLE V

(a) *Relationship between Duration of Bacteraemia and Fatality Rate*

Duration of Bacteraemia in Days.	1	2	3	4	5	6	7	8
Recoveries. . . . .	15	4	1	...	...	...	...	...
Deaths . . . . .	6	4	2	...	...	1	1	...
Total . . . . .	21	8	3	...	...	1	1	...
Fatality rate per cent..	28.5	50	66.6	...	...	...	...	...

(b) *Relationship between Duration of Bacteraemia and Blood Concentration of Sulphonamide*

Bacteraemia Days +ve.	Blood Level < 7 mgms./100 c.c.			Blood level > 7 mgms./100 c.c.		
	Total.	Deaths.	Fatality Rate (per cent.).	Total.	Deaths.	Fatality Rate (per cent.).
1	12	4	33.3	9	2	22.2
2	4	3	75.0	4	1	25.0
3-8	5	4	80.0	...	...	...
Total .	21	11	52.4	13	3	23.0

### SUMMARY AND CONCLUSIONS

Reference has been made to the importance of bacteraemia in lobar pneumonia as a factor of prognostic significance, and instances have been given of the extent of its effect on mortality. It has been indicated that, since the advent of sulphonamides in treatment, bacteraemia is no longer of such grave import as heretofore, although it still influences in no uncertain manner for a high fatality rate in pneumonia.

An attempt has been made to show that in patients with a positive blood culture there are certain factors which may be correlated with the final outcome, and so may be of considerable use in prognosis in such patients. In particular, stress has been put on the relationship which appears to exist between the duration of the bacteraemia, the blood level of the drug, and the leucocyte response, for it has been shown that in those who recovered a high blood concentration and leucocytosis was the rule, and that in such patients organisms rapidly disappeared from the blood stream. In contrast to this, among the deaths positive

blood cultures persisted in several patients for as long as five days, these patients having low leucocyte counts as well as low blood concentrations of sulphonamide. This would indicate that bacteriæmic patients who do not show a good reaction to the disease, as judged by the leucocyte response, are also incapable of maintaining a high level of the drug, which probably accounts for the persistence of organisms in their blood, and tends to perpetuate a vicious cycle to an untimely ending. Other factors to be taken into account in the bacteriæmic are the age of the patient, the degree of lung involvement, the type of infecting organism, the blood concentration of the drug, the duration of the bacteriæmia, the leucocyte response, and the leucocytic differential count.

It has been shown that a positive blood culture may persist for six or seven days, and that the longer the duration of bacteriæmia the worse the prognosis. In addition, the persistence of organisms in the blood stream tends to occur when the blood concentration of the drug is at lower levels.

The presence of positive blood cultures in patients suffering from pneumonia is, therefore, a factor of very considerable significance in prognosis. It is one which to some extent explains the varying fatality rates in different published series of patients with this disease, and it is obvious that before adequate comparisons may be made a knowledge of the constitution of any series with regard to the presence of bacteriæmia is of paramount importance.

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# THE PREVENTION OF MASTITIS: THE NURSING PROBLEM \*

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## ADMINISTRATIVE ARRANGEMENTS FOR THE CARE OF THE LACTATING MOTHER AT THE SIMPSON MEMORIAL MATERNITY PAVILION.

### ANTE-NATAL INSTRUCTION

THIS was originally given by the Senior and Junior Medical Officers in Charge of the Clinic. As these Clinics have grown considerably in numbers and the Medical Officers are very busy, it was found that they tended to overlook the importance of the breasts and were primarily interested in the detection of obstetric abnormalities.

Since January 1947 there has been a sister at each ante-natal clinic whose sole duty it is to examine the breasts and to give instruction in preparation for lactation.

The routine is as follows :—

- (1) All patients are seen at their first visit, the breasts examined and the history of any previous breast trouble taken. A note is made on the ante-natal card when to report again.
- (2) Patients with nipples tending to retract report back at the twenty-eighth week, or earlier if retraction is very pronounced. Thereafter they are seen at fortnightly intervals.
- (3) All other patients are seen at the thirty-second week. In this way all patients have their breasts seen at least twice during pregnancy by the sister, and more often as need arises.
- (4) The sister is present at the Infant Welfare Clinics to help with breast-feeding difficulties after discharge from hospital.

*The Lying-in Wards.*—Apart from the ante-natal ward, there are three normal lying-in wards, an isolation ward and one where women with venereal disease are delivered and nursed. These each have a nucleus of permanent nursing staff, with personal variations in technique, combined with frequently changing pupil midwives. There is a resident pædiatric registrar and a staff of daily visiting pædiatricians.

The actual conduct of breast feeding and the routine care of the breasts is very largely in the hands of the ward sister who is the link between the obstetrician (in charge of the mother's breasts) and the pædiatrician (in charge of the baby).

*The Infant Welfare Clinic.*—Mothers living within easy reach of

\* Read at a meeting of the Edinburgh Obstetrical Society, 8th January 1947.

the hospital bring their babies at regular intervals during the first year of life. Test feeding is arranged where necessary and a check is kept on the baby's and the mother's health.

A sister dietitian gives advice both here and in the ante-natal clinic and makes sure the mothers are obtaining all their priority rations. A lady almoner is also present to deal with social difficulties, and arrange holidays at a convalescent home where needed.

*Importance of Breast Feeding.*—Without entering into the old controversy of breast *versus* bottle-feeding, it may be taken that successful breast-feeding is the ideal at which to aim, largely because of the greater immunity to infection thereby conferred on the baby.

The great majority of hospital mothers will continue to breast-feed their babies if they realise this, and above all, if we can initiate and maintain lactation painlessly and adequately. But we have no right to advocate breast-feeding unless we take precautions to prevent mastitis.

*Causes of Mastitis.*—Mastitis is most often due to some lesion in the surface of the nipple, and the nipple with poor protraction is the more readily damaged. This lesion commonly occurs in the first fortnight, during or just after the first coming in of the milk (the engorgement stage) when the nipple is most prone to damage. The lesion may heal and yet mastitis supervene some days later, often after discharge from hospital. It has been suggested that the infection has entered at the time damage took place and lain latent.

Breast feeding should be virtually painless. If there is pain, there is damage either real or potential, so that pain, as always in medicine, is a warning. It is also no encouragement to a mother to continue breast-feeding.

*Damaged Nipples.*—However careful ante-natal preparation, many mothers will suffer from tender nipples at some time during the puerperium. Even through a lens it is not always possible to see anything abnormal, but if suckling is allowed to continue, the lens will later show (*a*) inflammation, (*b*) scattered petechiæ (often in a half-moon, (*c*) a small blister, or (*d*) a raw area on the nipple surface, a door of entry for every passing staphylococcus. If, in spite of the damage, suckling is continued, a genuine cracked nipple will develop, the crack often situated at the bottom of one of the normal furrows in the nipple, and recognisable by inflammation or bleeding. This may take several days to heal. The crack at the base of the nipple is relatively uncommon—it is the only one which might be attributed to the baby's bite.

*Explanation of Cracked Nipple.*—Nearly all damage to the nipple surface is caused by suction. Generally speaking, the well-shaped nipple with elastic areola is sucked well back into the baby's mouth, so that the sensitive tip has hardly any suction falling upon it. The poorly-developed nipple, with an inelastic areola, will remain in the front of the baby's mouth. In the same way, during the early days,



engorgement of the breast prevents this elasticity of the areola, and if suckling is permitted, a damaged nipple is the invariable result.

Both mothers and babies too, are often far from skilful and the baby not infrequently fails to open his mouth wide enough to obtain a good hold, or the mother draws back, not realising that a firm grip on the baby's part is the painless way.

A free flow of colostrum in the first few days will act as a lubricant in the process of suckling and is the precursor of freely flowing milk. Consequently there will be less danger of engorgement, as the surplus milk will tend to leak out.

### PREVENTIVE MEASURES

*Ante-Natal.*—Waller holds that the ideal breast for feeding a baby has (a) a thin elastic skin, (b) a reasonable nipple with good protraction, (c) an increase in size in pregnancy equivalent to 2-4 inches in chest measurement, and (d) a supply of colostrum easily expressed from several ducts. In this type of breast the milk will flow out easily and there is little risk of engorgement or cracked nipples. The expelling mechanism or "draught" reflex will come into action as early as the tenth to fourteenth day.

Ante-natal care can (a) improve the nipple protraction, (b) increase the ease of outflow of colostrum, and (c) render the unyielding breast somewhat more supple.

(a) Depending upon the degree of retraction, glass nipple shells (Fig. 1) should be worn for the last three to four months of pregnancy. These shells were originally worn to protect the mother's clothing during lactation, but are extensively used by Waller for the correction of retracted nipples. They consist of circular glass cups with a central hole fitting over the nipple (Figs. 2 and 3). Worn under a well-fitting brassière, they apply steady pressure on the breast and areola. The woman is instructed to wear them for a few hours daily at first, and then steadily all day. Most women wear them without discomfort or protest, and after a few weeks the improvement is often astonishing.

(b) and (c). As for increasing suppleness and ease of outflow ante-natally, the woman is taught to massage the breasts nightly with a little oil or liquid paraffin in the last couple of months.

She encircles the breast far back with both hands, thumbs on top, fingers underneath, and slides them firmly from periphery to areola about a dozen times. Then, supporting the breast with one hand, a little colostrum is expressed by pressure on the areola with finger and thumb of the other hand. The whole procedure takes less than five minutes daily and is easily taught. There is the added advantage that the woman can apply manual expression in hospital or after discharge as need arises.

The fear that it might lead to premature labour appears groundless. If the nipple area seems dry-skinned, lanoline ointment is of use.

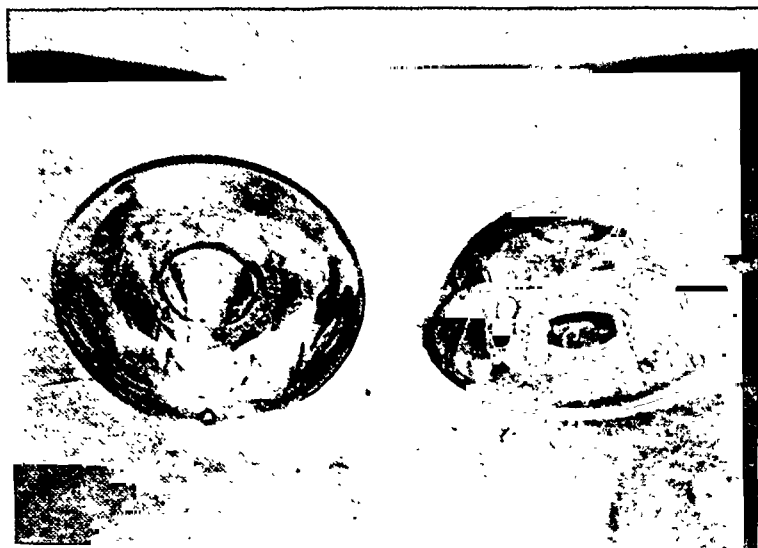


FIG. 1



FIG. 2



FIG. 3



FIG. 4

*In the Lying-in Wards.*—On the day after delivery a supporting breast binder should be applied.

The baby is put to the breast four- to six-hourly, and is allowed only a few minutes at each breast at first till the milk comes in.

About the second day the mother should begin to use the same breast massage and expression just before feeding-time. This will help to keep the breast tension low and the milk flowing freely.

If engorgement does occur, as it quite frequently does overnight or in the space of an hour or two, suckling should not be allowed for fear of nipple damage till the tension subsides and the baby can get a good grip.

Meanwhile, either the mother herself or the nurse should gently massage the breasts, though little milk can probably be expressed for a few feeds. The binder is firmly re-applied with rolls of cotton-wool under the breasts if at all pendulous. If permitted by the doctor in charge, stilbœstrol 5-10 mgm. (even 20 mgm. if there is very severe engorgement) given every four hours till ease is felt, is of very great value. The curtailing of the engorgement time is of great importance if the mother is going to preserve her milk supply. The stilbœstrol will damp down milk secretion considerably at first, but if expression, or as soon as possible, suckling be continued, the milk yield will rise again to normal in four to five days.

The control of tension will lessen the possibility of nipple damage, but it should be a rigid rule for nursing staff that no baby is allowed to feed if there is pain with suckling. The breasts should be expressed by hand (Fig. 4)—a procedure that should never cause the mother pain. A breast pump, working as it does by suction, does the very thing which should be avoided. A sterile dressing, preferably with an antiseptic ointment, should be kept over the nipples, and the baby given the breast milk by spoon or bottle till the nipple is-healed.

*Result of Ante-Natal Instruction.*—The above-mentioned methods of ante-natal instruction have been taught at one of the ante-natal clinics over a number of months, taking patients largely at random and watching the sequel in the several lying-in wards. The management in hospital varied from ward to ward, and the figures refer purely to the time spent in hospital.

The controls were taken from two wards—a normal lying-in and the Isolation Ward (67 and 33 patients respectively). A certain number of the pupil mothers developed puerperal pyrexia and were transferred to the Isolation Ward.

The pupil mothers had to attend the sister on two or more occasions till she was satisfied they were doing the treatment correctly. Those who came for one visit only (10) and did not report back have not been included, therefore the pupil mothers were presumably anxious to breast-feed. To offset this advantage, a certain number were referred by the Medical Officers on account of retracted nipples or difficulties with previous lactations.

*Nature of Complications Observed.*—(a) Damaged nipples, *i.e.* where suckling was temporarily suspended on this account; (b) severe engorgement, *i.e.* breasts tense, hard and painful—baby unable to suckle or obtaining negligible quantities of milk; (c) mastitis, *i.e.* flushed area on breast and pyrexia; (d) weaning of baby, because of breast difficulty or deficient lactation.

TABLE 1

	Pupils.	Controls.
Symptom-free lactation . . .	56	32
Complicated lactation . . .	44	68

TABLE 2

*Nature of Complications \**

	Pupils.	Controls.
Damaged nipples . . . .	29	36
Severe engorgement . . . .	3	9
Mastitis . . . . .	—	6
Weaning of baby . . . . .	4	9

\* Numerous patients recorded under more than one heading.

TABLE 3

*Adequacy of Lactation*

	Pupils.	Controls.
Mothers discharged with adequate lactation	83	64
Mothers discharged with inadequate lactation— <i>i.e.</i> babies requiring a complementary feed	13	27
Mothers lactating on discharge . . . .	96	91

TABLE 4

*Treatment of Retracted Nipples*

	Pupils.
Successfully treated with nipple shells . . . .	6
Not successful . . . . .	1

*Comments on Tables.*—To base results on such a small number of cases as 200 is not ideal. Especially is the incidence of mastitis in the Control group high; 4 out of the 6 cases occurred in the Isolation Ward, and two of the patients were definitely debilitated.

Even with careful ante-natal instruction, 44 per cent. of the mothers had difficulty with lactation, so that it is not an easy, natural function. Thus instruction must be combined with the most unremitting care and vigilance in the early days after the baby is born.

#### SUGGESTIONS FOR IMPROVEMENT IN THE PREVENTION OF MASTITIS

- (1) More attention in the ante-natal period.
- (2) Very much greater care in the puerperium, possibly supervised by the pædiatrician.

(3) Prompt treatment of painful nipple by cessation of suckling, sterile dressing, and manual expression of breast at each feeding time.

*Acknowledgements.* — Miss Ferlie, Matron, S.M.M.P., for much encouragement; Emeritus Professor Johnstone, for permission to work in his ante-natal clinic; Emeritus Professor McNeil for his unfailing support of breast-feeding; The Ward Sisters for permission to visit patients in their wards; and above all, Dr Waller and Sister Grose of the British Hospital for Mothers and Babies, Woolwich.

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## TREATMENT OF ACUTE PUERPERAL MASTITIS \*

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THE acutely engorged, tender, inflamed breast, occurring in the nursing mother during the first two weeks of the puerperium, depends for its pathology on two features: firstly, retention of milk in one or more lobules owing to obstruction of the corresponding ducts by clotted milk; and secondly, infection gaining access through a cracked nipple or simply along a duct lumen. Clotting is encouraged or initiated by infection, but usually begins in the stagnation of a faultily emptied breast. The acute mastitis, occurring usually about the ninth day of the puerperium, is an infective cellulitis; but the condition may be an aseptic inflammation when it appears earlier about the third day.

It follows that treatment must be along two lines: (1) To promote emptying of the breast by continuing suckling, or manually; or in some cases to suppress lactation altogether by synthetic oestrogens. (2) To prevent or combat infection. In 90 per cent. of cases the infection is due to staphylococcus aureus, and therefore this part of the problem resolves itself into the best method of using penicillin in this condition. Local penicillin is not indicated, and the circumstances are ideal for systemic therapy for there is an excellent blood supply to all parts of the inflamed closed lesion. It is therefore only necessary to determine the best time-dose relationship for the penicillin.

Two series of cases of acute puerperal mastitis treated with systemic penicillin have recently been reported. Hodgkinson and Nelson in America used a scheme of 25,000 units 3-hourly for three days; then 15,000 units 3-hourly for two days. Their 24 cases all resolved without abscess formation. Taylor and Way in Newcastle used 12,000-20,000 units for 3-10 days. Of their 10 cases, one went on to an abscess.

*Present Series.*—In the Simpson Maternity Pavilion of the Edinburgh Royal Infirmary in 1946 we were able to compare different methods of treatment. Altogether there were 50 cases of acute puerperal mastitis from 3500 deliveries (incidence 1.4 per cent.). Breast feeding was continued in all cases.

50 Cases:—

*Penicillin*, 40; all settled down.

*Sulphathiazole*, 5; 3 satisfactory: one where penicillin was apparently failing. Two unsatisfactory: one going on to abscess requiring incision; one not settling until given penicillin.

\* Read at a meeting of the Edinburgh Obstetrical Society, 8th January 1947.

*Fomentations alone*, 5; 4 satisfactory: 3 being in third day and possibly aseptic engorgement; one unsatisfactory, but responding to penicillin.

The penicillin cases, all of which settled, were in two contrasting series:—

30 Cases: 25,000 units 3-hourly for 48 hours-7 days (*i.e.* 200,000 units in 24 hours).

10 Cases: 100,000 units twice daily (12-hourly) for 48 hours-7 days (*i.e.* 200,000 units in 24 hours).

These series are too small to permit drawing significant conclusions, but as regards the two penicillin groups it was noted that equally good results were obtained with the less laborious method of two injections in the 24 hours. This appears to bear out the original contention of Florey, Turton and Duthie that for focal infections (as distinct from an active blood stream infection) 100,000 units 12-hourly should suffice. The drug is present in the local tissue fluids always for 8 hours, and for 12 hours in 50 per cent. of cases.

Penicillin treatment should be continued for at least 3 days, and until the temperature has settled below 98·2 F. for 48 hours. Sulphonamides need not be given concomitantly, but if the cellulitis does not rapidly settle, the possibility of a resistant staphylococcus should be remembered and a sulphonamide exhibited.

Fomentations are not advisable for they may macerate the nipple. The only local treatment needed is firm support in the form of a many-tailed binder with shoulder bands. It will be noted that suckling was maintained in this Edinburgh series. In the American series quoted lactation was inhibited; in the Newcastle series it was usually kept going. On the principle of putting an inflamed part at rest I personally favour inhibition of lactation by synthetic oestrogens.

The conclusion is that we should be quick to recognise the onset of puerperal mastitis—pain in the breast, headache, and slight elevation of temperature; and if penicillin is given promptly, then 100,000 units 12-hourly should abort the process.

I am grateful to Dr W. F. T. Haultain for letting me co-operate in the treatment of his patients; and to Dr Eileen Munn and Sister Somerville for carrying out the treatment.

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#### DISCUSSION

*Dr Fahmy* congratulated Miss Thomas on the work she was doing at the Simpson Maternity Pavilion in regard to the preparation of the breasts for satisfactory infant feeding. It seemed a sensible and practical plan to employ



the emptying of the ducts of the breast by gentle manipulation during the last weeks of pregnancy.

In regard to acute mastitis it was by no means rare for this condition to develop in the absence of any visible sign of cracking of the nipple, even though the most diligent search was made for such a possible source of infection. The women, however, frequently complained of pain in the nipple itself in the first few days of lactation, even when cracking was absent. If the nipples were very sore, then breast feeding should be stopped for a couple of days and the nipple treated. Dr Fahmy had found penicillin cream a very useful application to tender nipples whether cracking was present or not. In acute mastitis temporary arrest of breast feeding for a short period was probably a wise procedure. When headache was associated with a tender and painful breast, it was almost the rule to find a degree of pyrexia at the onset of the symptoms.

*Sister Myles* spoke of her three years' experience in a large maternity hospital in Detroit where they did not have one breast abscess. The patients were nearly all looked after by their own doctors before they came into hospital, so that they had no idea what ante-natal care they had had. Their care in hospital was the simplest *Sister Myles* had ever seen. The breasts were merely washed once a day, not before or after each feed. The breasts were supported by a suitable brassière and a soothing ointment used from the first day. The prevention of mastitis required careful attention to comparatively simple measures, such as helping the baby to "fix" properly so as to avoid trauma of the nipple and to facilitate emptying of the ducts. More ordinary cleanliness of mothers' hands and clothing rather than asepsis on the part of the nurse, hot bathing and regulation of fluid if acute engorgement developed were desirable.

*Dr Betty Sturrock* said that if breast feeding were going to be a success, hospitals should have the management of establishing it, and she thought that what *Sister Thomas* had told them was very important. She would like to see the expectant mother being taught a great deal more about breast feeding, for example, how to know if she had got enough milk or not. Complementary feeding by bottle should be avoided, and, if necessary, should be given by means of a spoon. Mothers on breast suckling rarely pleased a baby who had become accustomed to a bottle. In Edinburgh there existed a most hopeful field for co-operation between the hospitals and municipal health visitors in regard to the continuance of breast feeding.

*Dr Morris* agreed with *Sister Thomas* that a busy obstetrician was not the best person to inculcate ante-natal preparation of the nipples, but he could not agree with her when she said that the busy pædiatrician was any better. As ante-natal clinics were carried on at present, the medical officer in charge of the clinic had no time to look after these matters of education which must be made the responsibility of a midwife who was looking after only a certain number of patients at one time. He said he hoped they were going to hear from general practitioners about the incidence of mastitis. In the Ayrshire Central Hospital he had found an incidence of mastitis of between 4 and 5 per cent., and in domiciliary practice in the whole of Ayrshire the figure was but 2.5 per cent. However, many general practitioners had told him that his figures of 4 to 5 per cent. did not present the whole picture as they

found that in patients who had come home from hospital breast abscesses subsequently developed in an appalling percentage of cases.

Dr Morris said that in his experience it was rare to get mastitis without a previous eroded nipple. The importance of a cracked nipple was one which allowed ingress of the golden staphylococcus, not necessarily a gross crack but a tiny little thing, sometimes a little blister requiring a lens for its detection. Mastitis in hospitals came in epidemics, usually preceded by an outbreak of staphylococcal skin eruptions in the babies, followed by a run of cases of mastitis.

*Dr Ludlam* said that if the ward sister could get into direct contact with the health visitor she felt the latter would be able to help the patients with their breast feeding difficulties more than she could at present.

*Mr A. I. S. Macpherson* said that the paper he had published in 1943 dealt with cases of puerperal breast abscess admitted to a surgical ward, and the data regarding the incidence of cracked nipple were obtained by directly questioning the patients. A history of sore feeding and "the doctor said there was a crack" were alike accepted. In Dr Haultain's wards 80 cases of cracked nipple were followed up, all sore nipples being examined and all cracks graded according to depth, and in only two cases did actual breast infection supervene.

With regard to the treatment of mastitis, Mr Macpherson said he was sure that Mr Jeffrey would agree with him that the true effectiveness of penicillin was very difficult to assess. If the first stage in the pathology was stasis and engorgement, and it was only afterwards that the infection occurred, the very marked effect of administration of oestrogen on engorgement of the breast might well be calculated to abort an early mastitis, and the particular field for penicillin should be when oestrogens failed. He agreed with Mr Jeffrey that the twice daily administration of 100,000 units of penicillin was entirely satisfactory.

*Dr John Sturrock* said he agreed with Sister Myles that the answer to the question of prevention of mastitis was probably a simple one. Many experienced midwives of his acquaintance employing simple methods of instituting lactation produced admirable results. In the absence of rush or hurry, mother and baby had the best possible chance of mutual adjustment and breast troubles were minimised. Again the healthy environment of private practice probably rendered easier the uncomplicated healing of a cracked nipple. Regarding when to give penicillin, his own feeling was that it should be administered at the very first suggestion of a mastitis. Since using it he had been very satisfied with the results, and he agreed with Mr Jeffrey that it should be continued for at least two days after all clinical evidence of mastitis had disappeared. He still thought there was a place for hot applications in the initial stages of mastitis, if only for their symptomatic relief. As to the use of stilboestrol in promoting sudden arrest of established lactation, Dr Sturrock said his experience had been occasionally disquieting. Stilboestrol used in this way sometimes seemed to precipitate mastitis where there had been no evidence of it before deciding to stop breast secretion. It was, however, always perfectly satisfactory to prevent the establishment of lactation in a patient who was not to breast-feed.

*Dr Somerville* said he had enjoyed the papers read, and that he was a very strong advocate of breast feeding. In any epidemic it was the bottle babies that died, not the breast-fed babies. In general practice he had had satisfactory results in the treatment of mastitis by 12-hourly injections of penicillin 100,000 units.

*Dr Kennedy* agreed that mastitis arose without the previous existence of cracked nipple, and that it would be inadvisable to ask the pædiatrician to take over the care of the breasts.

*The President* thanked both speakers, and complimented Sister Thomas upon her lucid exposition of nursing technique and views. He would have wished that she could have been a little more explicit with regard to some details. For example, she had said she rubbed the nipples with oil, but what kind could one get these days? Perhaps she would mention this point when she replied.

Mr Jeffrey was one of the recognised experts on penicillin, and the President was glad now to have the opportunity of thanking Mr Jeffrey very much for his care of the cases of mastitis which had occurred in Ward 52 during the past year. He would like to ask one question: In what proportion of the cases in the wards was lactation stopped, and for how long?

The question as to who was to look after the breast seemed to be a very vexed one, and he thought it might be different in hospital and private practice because in the latter one had to look after the patient oneself, and the nurse in charge of the patient would look after the nursing under one's guidance. In hospital practice it was rather a different matter. Everybody was very busy, but he thought it might be best if the pædiatric sister was to supervise the breast feeding along with the ward sister.

Mastitis had always given rise to considerable worry not only in hospital but particularly after the patients had left hospital.

It would seem that a number of cases went to the surgical department three to four weeks after they had had their babies. These patients left hospital perfectly well, and he did not think the fault lay with the hospital. Between the time a patient left hospital and the time the health visitor took over there was often a hiatus, and he thought there should be some liaison between the ward sister and the health visitor so that the patient could be visited at once by the health visitor and nursing could be supervised exactly as it had been done in hospital.

He thought Dr Sturrock had been singularly unfortunate with stilbæstrol. His own experience had been quite satisfactory. He was very glad to hear Dr Betty Sturrock warning against unnecessary supplementary feeding and especially against the use of the bottle for this purpose. He had been preaching this for many years, but had had little success in persuading his pædiatric and nursing colleagues that it was one of the principal causes of early weaning.

*Sister Thomas*, in reply to discussion, said that the oil she had mentioned was "pale nut oil" or liquid paraffin. Briefly, the methods of prevention were—to express colostrum, advise the use of shields, and to keep the breasts clean.

*Mr Jeffrey* replied to the discussion.

## CLOSTRIDIUM WELCHII INFECTION OF THE PLEURAL CAVITY

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INFECTION of the pleural cavity by anaerobic gas producing bacilli is relatively common in cases of hæmothorax resulting from war wounds, and Elliott and Henry (1917) have described 87 cases from all of which *Clostridium Welchii* was isolated. This type of infection, however, appears to be extremely rare in civilian practice and I have not found a single case reported in the literature in this country. Porzecanski and Franchii (1936) reported one case following a gunshot wound of the chest, and in the case published by Bader and Müller (1939) *B. Welchii* was apparently introduced into the pleural cavity during thoracentesis. Lynch and Streider (1942) have published two cases, in the first of which *B. Welchii* was isolated only on one occasion from the hæmothorax fluid two days after a chest injury. Their second case appeared to have a hæmopneumothorax following a stab wound, and *B. Welchii* was isolated on three occasions. These were the only two cases of pleural infection by anaerobic gas producing bacilli seen at the Boston City Hospital in recent years, though many penetrating chest wounds were encountered. Finally, three cases were reported in 1944 by J. Karl Poppe, in all of which the condition followed an operation for lobectomy. In none of the above seven cases was there any evidence of a spreading gas gangrene, and recovery was universal. With regard to treatment, adequate open drainage was the most useful measure though penicillin, sulphonamides and antiserum were also of value.

The following case was encountered recently :—

N. M., aged 38, was admitted to the Royal Infirmary on 29th October 1946 with a history of illness since May 1945. He had been treated in a sanatorium, and tubercle bacilli were said to have been demonstrated in his sputum on one occasion. For some months he had had an empyema, which had been repeatedly aspirated, but the only bacteriological report stated that an anaerobic capsulated Gram-negative bacillus had been isolated, and this organism had not been investigated further. On admission to the Infirmary the patient was found to have a pyopneumothorax. This was treated by rib resection, and a large quantity of foul pus was evacuated. Subsequently, pus from the drainage tube was examined bacteriologically on several occasions and *Bacillus coli* was found. Later, it was decided to carry out a three-stage thoracoplasty operation, and a further specimen of pus, obtained at the first operation, was submitted for examination. This specimen contained *Clostridium Welchii* in large numbers. A few

days later a specimen of pus was again examined and *Clostridium Welchii* was isolated along with another anaerobic sporing bacillus. Large doses of penicillin were administered parenterally without marked effect, but the patient is making slow progress following second and third-stage thoracoplasty operations.

Bader and Müller (1939), suggest that *B. Welchii* infection of the pleural cavity is frequently the result of the organism being introduced during thoracentesis. This appears to be unlikely. Karl Poppe (1944) thought that in his cases infection may have resulted from a contamination of the pleural cavity by bronchial secretions during lobectomy, or from a bronchial stump following operation, the occasional presence of *Cl. Welchii* in the bronchial secretions having been noted by Farago (1935). The latter carried out some interesting work performing autopsies on thirty men dying of tuberculosis and isolating *B. Welchii* from the tuberculous lung cavities in every case. He did not consider that there was any possibility of these being post-mortem blood stream infections and proceeded to demonstrate *B. Welchii* in the sputum of 12 per cent. of tuberculous patients with definite cavitation. This latter finding appears to be of some significance as both Branham (1927) and Levinthal (1928) failed to find *B. Welchii* in the mouths of normal people. Farago also examined 21 sera from patients with tuberculous cavitation of lungs, and found that 42·8 per cent. inhibited both the hæmotoxin and the exotoxin of *B. Welchii*; 17 control sera failed to inhibit the toxins.

SUMMARY.—A case is described in which *Bacillus Welchii* was demonstrated in the pus from a pyopneumothorax. The relevant literature is briefly reviewed, and the possible sources of infection in such cases are discussed.

I am indebted to Mr Walter Mercer for permission to publish the case notes, and to Dr W. R. Logan for his help and advice in the preparation of this paper.

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## SOME IMPRESSIONS OF AMERICAN MEDICINE \*

By J. L. HENDERSON, M.D., F.R.C.P.ED.

I WAS fortunate to have the opportunity of spending last year in the United States, and I have been asked to speak to you to-night about some impressions of American medicine. I am not qualified to give an authoritative survey of American medicine, because the United States is so vast and I saw only a small part of it, and also, because I spent most of my time in a few of the most famous medical centres, which, no doubt, have higher standards than most. I remained for most of the year in the North East, and I think it desirable that one's impressions should have been derived from that part of the country which is the most cultured and the most stable, assertions which Americans from elsewhere would hotly contest. I spent most of my time in New England, at the Harvard Medical School in Boston, and the Yale Medical School in New Haven. I also worked for a considerable period in New York, that great cosmopolitan city which most Americans disclaim as truly American. I visited several other medical centres, each for a short period, including Johns Hopkins in Baltimore; Cincinnati, Chicago and the Mayo Clinic in the Middle West; and Toronto in Canada.

The object of my visit to the United States was to observe the practice of American pædiatrics in its widest sense, rather than concentrate on one or two research projects.

### MEDICAL PRACTICE

*Qualifications.*—Medical qualifications are not uniform throughout the country, but are rapidly tending in that direction. Each of the forty-eight states has its own licensing body. Formerly, doctors holding a state licence were not permitted to practice in any other state, except in those with reciprocal licensing arrangements; such agreements between states were common. Now forty-four of the forty-eight states acknowledge a national qualification, known as the National Medical Board Qualification, and the majority of American medical students now take this qualification rather than a state qualification, although they still require a state licence. This enables the medical authority of each state to decline to license anyone they consider undesirable. The national qualification cannot be taken until candidates have spent one year on the resident staff of a recognised hospital after completion of the medical course—an excellent provision. Many of the states do not require this year of hospital experience

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before permitting their state qualification examination to be taken. What is the position regarding American citizens who study medicine abroad? The great majority of them have either failed to gain admission to an American Medical School, often on racial grounds, or, having been admitted, are eliminated during the course, and most of them go to European schools, particularly British extra-mural schools. They must, of course, take a state qualification when they return to the United States, but they are ineligible for the National Medical Board qualification. Some states discriminate against graduates of certain foreign medical schools: the State of Connecticut does not consider a graduate of any British extra-mural school eligible for a state licence; several of the Middle West States will not admit graduates of Central European schools, and the Western States debar those from Mexican and Cuban schools. In the latter two instances, these regulations are directed principally against immigrants.

The standard qualification granted by American medical schools at the end of the four-year course is the degree of Doctor of Medicine.

The higher qualifications in American medicine consist of the various Specialist Board Diplomas, such as those in medicine, pædiatrics, neuro-surgery, etc. These may not be taken until considerable experience of a specified type has been obtained.

*General Practice.*—General practice in small towns and in rural areas is much the same as in this country, but in large towns there is more specialised practice, particularly in pædiatrics. Every large town has many pædiatricians who restrict their activities to children, and the care of children in health and disease is mostly undertaken by them.

*Group Practice.*—The great distance between large towns with important medical centres, in this vast country, has favoured the development of group practice, which is more prevalent than in Britain. In small and medium-sized towns one often finds a firm of several doctors each specialising in a particular branch of medicine. This would seem to raise the standard of medical practice, but to lower the standard of specialist practice.

*Consultant Practice.*—Many American consultants have their consulting rooms in the hospitals to which they are appointed, and treat their in-patients in the private units of their hospitals. They thus have the best laboratory, technical and nursing facilities for their private work, advantages which are denied to most British consultants.

## AMERICAN HOSPITALS

*Architecture.*—Most of the new American hospitals cover a relatively small area and have from six to fifteen or more storeys, even in cities like Boston and Toronto where skyscrapers are exceptional. The projected new children's hospital of 540 beds in Toronto is to have twenty storeys, and the new Boston children's hospital twelve.

I think that compactness resulting from building upwards rather than spreading over a large area has several advantages, the chief being cheaper building and maintenance and easy accessibility of all parts of the hospital.

American hospitals are often rebuilt after twenty to thirty years, so many of them are more modern than our own. The tendency everywhere in hospital planning is towards smaller wards, a most desirable reform which is specially important in children's hospitals and hospitals for infectious diseases. In modern children's hospitals most of the infants and children under two years are provided with individual rooms, a considerable proportion of those between two and six years with individual cubicles, and those between six and twelve years with small wards. Separate rooms with glass partitions to prevent a feeling of loneliness, are a much better safeguard against cross-infection, which is such a menace in infants' units, than cubicles. I was interested to find that more provision is being made for adolescents in modern children's hospitals than in the past, and units are now being provided for children between twelve and sixteen years. Neither pædiatricians nor physicians have taken much interest in this age group in the past; it is surely wrong to debar children of over twelve years from children's hospitals.

I was impressed by the value of the large medical centre which caters for all types of patients. It is a great advantage to be able to consult specialists in any branch of medicine, personally, about a case; to have every diagnostic and therapeutic facility at hand; and the case records of patients, who may pass from one unit to another, are readily available. Perhaps, most important of all, it is a great advantage for those engaged in the various branches of medicine to have joint discussions, and to meet together in the hospital canteen. Moreover, valuable time is saved by not having to travel from one hospital or department to another in a large city.

The question is often asked whether it is better to have small specialist hospitals, or special units in a large hospital. I found that some of the best pædiatric clinics were smallish units in a large general hospital, as at Yale, Johns Hopkins, and the Presbyterian Hospital. I think that unless a children's hospital has 300 beds or more, as at Boston and Toronto, it should be a unit of a general hospital to enable it to embrace facilities which a smaller hospital cannot afford.

I was interested to find that infectious diseases of all kinds are being treated in an infectious diseases unit in many American general hospitals, rather than in special fever hospitals. This practice has the great advantage of enabling physicians and pædiatricians to be much more familiar with infectious diseases and their complications, and perhaps the patient may gain from less highly specialised supervision.

*Equipment.*—Foreign visitors to American hospitals are all greatly impressed by the lavish provision of facilities and equipment of all kinds, though most of them, like myself, realise, after becoming



acclimatised to the American way of life, that these assets also have their disadvantages. They are apt to be used routinely rather than intelligently, and I feel that such extravagant and undue reliance on scientific aids is not good training for students and young graduates. Nevertheless, these tools of medical practice all have their value if correctly used, and the hospitals in this country have fallen behind those of America in this respect.

*Staff.*—The main difference in the constitution of the staff of American and British hospitals is the much larger size of the resident house staff in American hospitals, a feature I will discuss along with medical education. Each service of a hospital is presided over by the member of the senior staff who is the professor in the university. In medicine, for instance, he is called the physician-in-chief; he usually holds a weekly meeting with all the members of the permanent staff of his hospital department, and also a weekly meeting with the medical superintendent, the chairman of the board of managers, and the head of each of the other hospital departments. The permanent staff do not remain attached to a ward permanently, as in this country, but rotate, usually at intervals of several months. This enables them, occasionally, to have a period without ward duties during which time more attention can be given to research.

The nursing arrangements do not differ much from our own. There is an acute shortage of nurses in the United States, as in Britain, and the hospitals are having great difficulty in maintaining the normal establishment of staff nurses.

There is a great disparity in the numbers of ancillary staff between British and American hospitals. Most American hospitals have several dietitians, many almoners, and hosts of technicians and secretaries. There is no gainsaying the fact that an efficient teaching hospital should have a much larger ancillary staff than most of our hospitals have been provided with in the past.

*Administration.*—Large American hospitals are administered by a medical superintendent, as in this country, and there is usually a deputy superintendent also. The post of deputy facilitates the training of young men as hospital administrators. Perhaps we should pay more attention to the training of hospital administrators, for the efficient running of a hospital calls for great experience and wisdom.

*Maintenance Costs.*—The cost *per capita* of maintenance in American hospitals is very much higher than in this country. The services provided are elaborate, but one feels that the advantages accruing to the patient are not commensurate with the high cost of hospital treatment. The cost of maintenance in the New Haven hospital, for instance, is £2, 15s. per day, and in the Boston Children's Hospital £2, 5s. per day. These hospitals have a flat rate of £1, 15s. and £1, 10s. per day respectively, adjustable according to the ability of the patient to pay. In comparing these costs with 18s. per day in the Edinburgh Royal Infirmary, and 13s. per day in the Royal Edin-

burgh Hospital for Sick Children, it must be emphasised that incomes and the cost of living are approximately twice as much in the United States as in Britain. The cost of maintenance is, of course, higher in the private hospital units.

### MEDICAL SCHOOLS AND TEACHING HOSPITALS

*Unification.*—The modern tendency to have the buildings of a medical school located on the same site as those of a large medical centre seems commendable. Such close proximity encourages liaison between the non-clinical and clinical departments, and students are spared the inconveniences of travelling from one hospital or department to another. Building developments in recent years have usually been inspired by this principle in this country, as well as in the United States, and we see its fulfilment at Aberdeen for example.

*Research Facilities.*—The research facilities in American medical schools and teaching hospitals are the envy of the rest of the world. Laboratory accommodation and equipment are lavish, and experimental animals abound in the leading schools. Favourable economic circumstances would appear to be the principal reason for this pre-eminence, but not the sole reason. The individualism, enterprise, and enthusiasm of the American are all contributory. I think too much insistence is sometimes placed on the publication of a large number of papers to justify the provision and maintenance of such costly facilities, and the principle of insisting on research workers publishing a certain number of papers a year is unsound. It encourages premature and unnecessary publication and the common practice of publishing the results of an investigation in several small papers. We also have these shortcomings, but, I fancy, to a lesser extent.

### MEDICAL EDUCATION

*Central Authority.*—Over forty years ago the American Medical Association assumed control of American medical education by appointing a Council on Medical Education. The Association of American Medical Colleges became closely linked with this Council, and other educational and hospital bodies were later co-opted. An Annual Congress on Medical Education and Licensure is held in Chicago each February. This body has raised the standard of medical education in America by insisting on the maintenance of a prescribed standard in medical schools. The schools are classified as Approved, Unapproved, and Schools on Probation. The one Unapproved school, which was the largest in the United States, has recently been closed. There are no schools on Probation at the present time, but, occasionally, a school is warned of the possibility of its degradation.

*Number and Size of Medical Schools.*—There are seventy-two approved medical schools in the United States. Most of them limit the number of students to 70 to 100 a year. A few have more. The

University of Pennsylvania is probably the largest with about 140 a year. Harvard has about 115 a year, and Yale only 55.

There is no doubt that the smaller the class the better the educational opportunity for the student. This applies particularly to practical laboratory work, and to the clinical subjects. Also there is more opportunity for personal contact between teacher and student. I found American medical educationists very critical of the large classes which we have in some of our schools, notably Edinburgh, and appalled at the enormous size of the classes in some Continental schools.

*Entrance Qualifications.*—All applicants for admission to American medical schools must have had a university education. Two or three years of college life before entering a medical school is highly commendable, particularly when the education is broad and embraces the arts.

Qualifications of a specified standard in pure science and biology are necessary prerequisites. This enables these subjects to be excluded from the medical curriculum which, consequently, is completed in four years, two pre-clinical and two clinical. Clinical teaching is usually commenced in the second year.

American medical students are, on the average, two to three years older than British medical students, because they have already spent two or three years at college. The average age of qualification is twenty-five to twenty-six. One felt that these additional years were a considerable asset, not only because they had enabled the student to have a basic general university education, and experience college life, but chiefly because of a more mature outlook and a greater capacity for steady work.

*The Curriculum.*—In a few of the more progressive American medical schools courses of systematic lectures have been considerably curtailed, or even abolished, in recent years. One feels that some curtailment of our contemporary, overloaded curriculum is desirable, but complete abolition of systematic lectures deprives the student of a co-ordinated framework on which to build.

The time allotted to the various subjects in the medical curriculum is much the same in the two countries. The considerably greater amount of time devoted to the teaching and practice of biochemistry in the United States is fully justified, as biochemistry now occupies such an important place in modern medical thought and practice. In some of our schools one feels that more time might be spent on biochemistry at the expense of a curtailment of the large amount of time devoted to anatomy.

The Yale Medical School probably has the most revolutionary curriculum of any in the United States. Didactic teaching has been greatly curtailed, no record of attendances is kept and class examinations are optional. There are no systematic lectures in the clinical subjects, but there is a weekly clinical lecture in medicine, surgery, obstetrics, pædiatrics and psychiatry throughout the two clinical

years. Though I would prefer modified courses of systematic lectures to provide a co-ordinated framework and co-ordination between scientific and clinical teaching as in Edinburgh, the Yale system has much to commend it. The student's character and ability are stimulated by leaving so much to his honour and initiative. There is too much spoon-feeding and not enough opportunity for individual initiative and development in our large schools with their heavily loaded curricula.

More joint staff-student discussions are arranged in American schools. They help teachers to understand the student's outlook and to appreciate his problems, and the student gains a fuller insight into his teacher's philosophy and is stimulated by closer contact and fellowship.

The clinical teaching and clinical material is not well balanced in the principal American schools such as Johns Hopkins, Columbia, and Harvard. There is too large a proportion of patients with uncommon diseases in the teaching hospitals of these schools, and the interest of the highly specialised staff in these rarities stimulates the students to take a disproportionate amount of interest in them. One has sometimes deplored a similar tendency in our own schools, but this imbalance would seem to be much greater in the leading American schools.

I was disappointed to find that none of the medical schools I visited had adopted the system of close integration of scientific and clinical teaching, which has been such a conspicuous success in the education of our third-year students in Edinburgh.

*Laboratory Facilities.*—The facilities for practical work are better, as a rule, in the United States than in Britain. This is important, as experience in various branches of laboratory and experimental work is of great value in the training of a doctor. It fosters a more scientific and critical attitude of mind, and it develops manual dexterity.

*Library Facilities.*—Each of the medical schools I visited had a large general medical library containing a good range of text books and all the principal periodicals. I was impressed by the way in which the students' convenience was studied and by the amount of use which students made of these facilities. The libraries are open until 10 p.m. or even 10.45 p.m., including Saturdays, and on Sundays from 2 p.m. until 6 p.m. or even 9.30 p.m. as at Yale. Our medical libraries are closed at 5 or 6 p.m. and are closed on Saturday afternoons and Sundays.

The degree to which students can use a medical library during the day depends on the loading of the curriculum. If heavily loaded, as in Edinburgh, the need for the medical library to be open at night, and at the week-ends, is all the greater.

In schools with a less heavily loaded curriculum, such as Yale, I was impressed by the intelligent use made of the library by students. The habit of referring to the relevant literature when studying clinical

cases is fostered and becomes a regular practice of the keener student. Such a habit is a keystone of intelligent medical thinking and cannot be cultivated too early. If it is not developed during the student years it most likely never will be.

### CLINICAL EXPERIENCE

(1) *Students*.—Students in American medical schools are allotted much more individual clinical work than it is possible to give in our larger schools. A small group of perhaps six students is allotted to a clinical service in each branch of medicine in turn. During this period, these students, in rotation, take the histories of all admissions day and night, record the clinical examination and assist in investigation and treatment. In the final year, the students are similarly allotted to the various out-patient clinics where they work individually after taking the history and conducting the examination each case is discussed with a member of the staff, and students follow-up their patients on return visits.

The opportunities for individual work are a valuable adjunct to routine clinical teaching in the wards. There can be little doubt that given a limited number of students, and adequate accommodation and facilities for students to work individually, particularly in out-patient departments, students learn clinical medicine much more readily by individual practice and stimulus than by listening, as one of a group to others relating the history and demonstrating the features of a case.

(2) *Graduates: the Interne System*.—This is an extremely valuable feature of American medical education which has now become widely adopted in the United States. It implies one year's hospital experience after the completion of the four years medical course, and this year is a necessary qualification for eligibility to sit the third part of the National Board qualifying examination (the first part is taken at the end of the second year of the medical course, and the second part at the end of the fourth year).

An interne is a junior resident medical officer. There are three grades of resident medical officer in American hospitals. There is one senior resident, there are a few assistant residents and there are numerous internes (about 66-75 per cent. of the resident medical officers are internes). Most of the routine work is done by the internes who thus have an excellent opportunity of gaining proficiency in clinical medicine under expert supervision. The year's internship may be spent in any branch of clinical work chosen by the student, and experience in various branches of clinical work is often obtained during the year. The State of Pennsylvania insists on candidates taking rotating internships covering medicine, surgery, pædiatrics, and obstetrics, for its qualification. The result is that few doctors not trained in Pennsylvania are eligible for its state licence.

All acknowledge the great value of a period of apprenticeship

such as is provided by the interne system, and there is welcome approval in this country of the Goodenough Committee's strong recommendation that a similar system be adopted in Britain. It is a sad reflection that so little use had been made, in the past, of the abundance of clinical material in our hospitals for apprenticing doctors.

### POST-GRADUATE EDUCATION

Many of the observations regarding undergraduate education also apply to post-graduate education. The advantage of good library and laboratory facilities is particularly important in this sphere of medical education.

*Value of Large Resident Staffs in Selection of Talent.*—The large establishment of resident medical officers in American hospitals provides an excellent opportunity for the selection of talent. The more able men are chosen from the interne group and promoted to the rank of assistant resident, and the most able of these is promoted to the rank of resident. Our system does not provide the same opportunity for the selection of talent.

*Value of Large Resident Staff in Providing Opportunity for Studying Clinical Material.*—The size of the resident staff not only provides a valuable apprenticeship for most American students of medicine immediately after completion of the medical curriculum, but also time for each apprentice to study his cases and the diseases they exemplify more thoroughly. Our system of having one resident without any, or, occasionally one, assistant resident, has deprived most of our new graduates of an irreplaceable clinical training. The fortunate ones, who are granted this opportunity, have not the time to do their routine work as thoroughly as desirable for a trainee, and no time to study the relevant literature, and thus do not learn as much from the patients under their care as they could if given a reasonable opportunity.

*Value of Long Resident Training of Specialists.*—The resident medical officers who are promoted because of their ability from the junior grade of interne to assistant resident, and then resident, have continuous clinical experience for three or four years in medicine, the same in pædiatrics and longer in surgery. Some time may be spent in laboratory work such as pathology, bacteriology or biochemistry between the appointments of assistant resident and resident.

The resident's duties are largely supervisory and administrative and he may have between ten and twenty assistant residents and internes (mostly internes) under his direction. This long resident training with increasing responsibility and opportunity provides an unrivalled basic training for specialists.

*Organised Post-Graduate Courses.*—These are not a feature of American Post-Graduate education except in special fields such as Public Health. There is less need for organised courses of instruction

in the United States than in this country, because of the much greater number of resident and non-resident hospital appointments, and the excellent laboratory, clinical and library facilities offered to post-graduates. Although the opportunities for advanced post-graduate study are excellent, one feels that the American schools would be performing a valuable additional service to medical education by inaugurating organised post-graduate courses. The guidance thus offered to post-graduates, and a well-balanced presentation of contemporary theory and practice would allow a much greater number of graduates to benefit from the unrivalled educational facilities of the leading American clinics.

### NURSING EDUCATION

In the United States a nurse's training occupies three years. The training is a comprehensive one and includes obstetrics, pædiatrics, infectious diseases and psychiatry, all of which are excluded from a general nurse's training in this country. This system gives pupil nurses a broad though somewhat superficial education in the whole field of nursing, but the concentration of so much theory into three years entails a regrettable deficiency of practical training. Such a comprehensive nursing education has many advocates in the nursing profession in this country, and may ultimately be introduced here.

Nursing education is more closely identified with universities in the United States than in Britain, and many American nursing schools are university departments. The student nurses graduating from such schools receive a degree. Two American university schools of nursing will only admit university graduates, and the aim of these schools is to train teachers and administrators rather than practical nurses. I disagree with this principle because one cannot select good nurses before they begin their training. Contrary to the practice in this country, American student nurses are unpaid and tuition fees and living expenses for the three-year period cost a nurse about £300. After qualification a nurse receives a salary of about £500 exclusive of living expenses. This is comparable with the remuneration of British nurses when allowance is made for the higher cost of living in the United States.

### AN AMERICAN NATIONAL HEALTH SERVICE ?

Last year a National Health Service Bill called the Wagner-Murray-Dingle Bill was presented to the United States Congress. Its provisions were less comprehensive than those proposed in the first British White Paper on a National Health Service. Much evidence was obtained by the Committee appointed to consider the measure, and the "Hearings" in Washington lasted many months. There is little chance of the passage of such a Bill in the United States Congress and Senate at the present time, because the country is enjoying prosperity

and is, therefore, in no mood for radical reforms. I was told that such a measure would have had a fair chance of success if it had been introduced as part of President Roosevelt's New Deal Legislation in the middle 'thirties.

The great majority of American doctors led by The American Medical Association are bitterly opposed to the Bill, but most other people appear to be indifferent. I need hardly emphasise the extreme complexity of evolving a Federal Health Service in such a vast and diversified country as the United States.

I cannot close without expressing my sincere gratitude for all the kindness and bountiful hospitality I enjoyed in the United States, that great country which has a common heritage with our own.

### DISCUSSION

*Dr Traquair* said that his own experiences of America had been extremely short, but one could sometimes pick up a good deal of information on a short visit. American students who obtained their training in the School of Medicine of the Royal Colleges of Edinburgh took relatively high places in the State examinations on their return to America. The title "Resident" in America had not the same meaning as Resident in, for example, the Royal Infirmary of Edinburgh. In America the Resident was a graduate who had had five years post-graduate hospital training, often including foreign experience, and was qualified to hold a high hospital post.

American hospitality was always overwhelming and often embarrassing.

One was struck by the lavish equipment of many of the hospitals and their operating theatres. On the other hand, he remembered the simple furnishings of the theatre in which Harvey Cushing did his famous brain surgery, showing that it is the man and not the equipment that does the work. He specially called to mind one hospital which had no source of heat of its own. Steam was brought in from a nearby factory through a meter, as we would lay on electricity or gas, and by this means all the heating, cooking, washing, sterilising and so on of the hospital were done.

The proportion of doctors to patients, especially in the large out-patient departments, is much higher than in this country owing to a different method of organisation of the hospital staff.

*Mr Dott* said it was a good while now since he had been in the States, but he remembered with utmost gratitude the hospitality of the Americans. He said he owed a deep debt of gratitude to America in having been the holder of a Rockefeller Foundation Scholarship. He said he thought Dr Henderson had given an excellent and understanding account of medical conditions and activities in the States, with due emphasis on the many advantages and few disadvantages that obtain there.

*Dr Peterkin* said he had three years' experience of Americans abroad and had an association with several hospitals from various places, such as Harvard, Detroit and Minnesota. He spoke highly of these schools, especially the University of Minnesota. Many Americans thought the new schools better than the old established ones. Undoubtedly too many American doctors relied on laboratory tests rather than clinical acumen.



*Dr Douglas Robertson* said that one must agree that American medicine generally is of a high standard, but he thought that there is a regrettable tendency towards over-specialisation, with a consequent virtual disappearance of the general practitioner—the man with an all-over view of the patient. He felt that too much reliance is placed on laboratory tests and too little on the clinical examination of the sick person.

*Mr Lowdon* referred to Dr Henderson's statements that Yale University admitted only 55 medical students each year and that the same University had adopted a revolutionary system of teaching almost without systematic lectures. He asked how the selection of 55 students from the presumably large number of applicants was made, and whether the success of the new system of teaching was not dependent on the fact that these students were of ability above the average.

*Mr Pollock* said that he would like to take the opportunity of thanking Dr Henderson for his very excellent portrayal of medical conditions in America. From a personal experience of more than five years' duration, during which he had passed through the grades from Interne to Assistant, he could confirm all the points which the speaker had made.

In regard to the training of nurses, he agreed that too much emphasis was placed on the technological side of their curriculum to the detriment of practical nursing. He hoped that in this country we would in the future concentrate on the latter aspect rather than on the production of a laboratory technician.

Dr Henderson's description of the facilities provided for Residents in American hospitals was one of the finer features of the training in that country, and the fact that most medical men availed themselves of these opportunities before launching into remunerative practice was a custom which could be followed with advantage in Britain, both to the doctor and to the patient. This interest in post-graduate study was perhaps a result of the happy liaison between teacher and student. Every American student had an *entre* to his chief, and could obtain his advice and help in a way which did not exist in this country.

It gave him great pleasure to associate himself with Dr Henderson in testifying to the excellence of the training of medical students in America and to the kindness and help he himself had received while a Resident in the States.

*Dr Henderson* replied and said he had a few more remarks to make about nursing. One's impression was, although it was difficult for a doctor to judge, that the standard of American nursing is inferior to the British. It is the policy in some American nursing schools to attempt to teach pupil nurses a good deal about disease and treatment, consequently they tend to have a lot of theoretical teaching at the expense of practical training. He thought it undesirable to attempt so much theoretical teaching in a nurse's training. Attendant nurses, who have a training of fifteen to eighteen months and are licensed, are often preferred to fully-trained nurses in the United States, because they are almost as competent in the art of nursing and they are more willing to help with domestic work. He thought the introduction of a comprehensive system of nursing education in this country likely, though many would regard it as a retrograde step. A considerable proportion of the

nursing profession in Britain favours such a system of training, but the older members of the profession are opposed to it. The younger members of the profession maintain that a student nurse who wishes to have a qualification in two or three branches of nursing cannot be expected to spend five or six years in training as at present.

He emphasised that the Resident in American hospitals is a very select person with several years of clinical experience. He agreed that Americans are inclined to over-investigate their patients, without using enough judgment in the selection of procedures which are likely to prove helpful.

Regarding Mr Lowdon's question about the selection of Yale medical students, he said there are about 1500 applicants a year, and consequently only those, who had distinguished themselves at school and college are selected. Each of about 200 screened candidates is interviewed by three individual selectors. It is chiefly because of the careful and rigid selection of students that the Yale school is able to have such a liberal system of education. Such a system would not be a success in Edinburgh with its large number of younger students.

## NEW BOOKS

*A Synopsis of Anæsthesia.* By J. ALFRED LEE, M.R.C.S., L.R.C.P., M.M.S.A., D.A.  
Pp. vi+254, with 42 illustrations. Bristol: John Wright & Sons Ltd. Price 12s. 6d.

This Synopsis fully justifies the claim made by the author regarding its suitability as a source of reference and a revision summary for examination candidates. The contents have been extracted from a very complete range of the literature on anæsthesia, and although there is much compression of the matter, the various methods of analgesia and anæsthesia are set out in commendably clear detail and logical sequence. This book can be recommended with confidence to all anæsthetists but particularly those who are preparing for examinations and those who have to teach undergraduates.

*The Renaissance and its Influence on English Medicine, Surgery and Public Health.*  
By SIR ARTHUR S. MACNALT, K.C.B., M.D., F.R.C.P. Pp. 30, with 4 illustrations.  
London: Christopher Johnson. 1946. Price 5s.

It was not until the value of Greek thought became manifest to the practical Englishman that the influence of the Renaissance became widespread, and the new movement reached its height in Tudor times. In the days of Thomas Vicary who, in 1540, received from Henry VIII the Act of Union between Surgeons and Barber Surgeons, the country was prosperous and the standard of nutrition was high. Nevertheless bubonic plague and sweating sickness levied a heavy toll, and reduced considerably the population, then about five million. The worst plague epidemic of the century was in 1563-4, when a thousand persons died weekly in London. As for the sweating sickness, it swept through England in a series of epidemics, the last of which appeared in 1551, when it was described in a treatise by John Caius. There was great need for reform in matters affecting public health, and the leading pioneer was Sir Thomas More (1478-1535), the citizens of whose *Utopia* (1516) esteemed health as "the greatest of all pleasures." He envisaged communal meals, nursery schools, industrial welfare, eugenic mating and, in fact, many of the aspirations of to-day. Henry VIII showed little discernment when he sent More to the scaffold. Other writers on public health and hygiene were Sir Thomas Elyot whose *Castel of Health* appeared in 1534, and the quaint physician and traveller Andrew Boorde who published his *Breviarie of Health* in 1547. Linacre's foundation of the Royal College of Physicians in 1518 gave a strong impetus to medical education. Vicary performed the same office for surgery and thus the doors were opened to the light of the Renaissance.

*Whither Medicine: from Dogma to Science?* By A. FIDLER, M.D. Pp. ix+115.  
Edinburgh: Thomas Nelson & Sons. 1946. Price 6s. net.

The purpose of this book, says the author, is to examine critically the implications and consequences of the materialistic theory in medicine. He starts by enquiring what is meant by "normal" and "abnormal" and seeks to determine the nature of structure and of function, and then goes on to study the medicine of probability. He is critical of present methods of presenting and analysing data, and offers a new scheme which he believes will prove a better method for scientific and practical purposes. "When one looks at the existing magnificent hospitals, medical institutions and laboratories and thinks of the multitude of investigators working therein without a clear-cut aim or method to guide their research and only blinded by their modern equipment, which by itself can provide no fruitful results, one cannot help feeling the tragedy of so much wasted effort. The medicine of probability provides the clear-cut aim."

## NEW EDITIONS

*Textbook of Medicine.* Edited by SIR JOHN CONYBEARE, K.B.E., M.C., D.M., F.R.C.P. Eighth Edition. Pp. xx+1170, with illustrations and 31 X-ray plates. Edinburgh: E. & S. Livingstone. 1946. Price 30s. net.

Conybeare's *Medicine* has long held a prominent place amongst the doctor's books and the present edition maintains the high standard of its predecessors. The present volume includes a section on penicillin and much new information derived from war experience has been included. The textbook should continue to appeal to undergraduate and practitioner alike.

*The Care of the Aged.* (Geriatrics.) By M. W. THEWLIS, M.D. Fifth Edition. Pp. 500, with 65 illustrations. London: Henry Kimpton. 1946. Price 40s. net.

At the present time a much larger proportion of the population are living beyond the age of 60 and the subject of their care is becoming of increasing importance. Some of the disorders to which old people are subject are peculiar to their years: others which also may occur in younger individuals raise special problems in the aged.

The author, who has been assisted by a number of experts, deals not only with the diseases of the ageing but also with many geriatric problems—hygiene, hobbies, medico-legal questions, surgery, anaesthesia, alcohol, etc. This important subject is one which should receive greater attention from the profession and this valuable treatise with its wealth of information can be thoroughly recommended.

*Leprosy.* By SIR LEONARD ROGERS, K.C.S.I., C.I.E., M.D., F.R.C.P., F.R.C.S., F.R.S., I.M.S., and ERNEST MUIR, C.I.E., M.D., F.R.C.S.E. Third Edition. Pp. xii+280, with 88 maps, charts and illustrations. Bristol: John Wright & Sons Ltd. 1946. Price 25s. net.

This book is familiar to all interested in diseases of tropical climates and the third edition, appearing six years after the last, will receive the welcome due to a standard and authoritative work. The general arrangement is that of the second edition but with elaboration of certain important points and a number of additions, notably on the improved technique for the lepromin test and the trial of new and promising drugs in treatment. All aspects of the disease are treated in a manner calculated to afford the maximum of information in the minimum of space. The text is supported by 88 maps, figures and reproductions of photographs. The value of the latter is enhanced by the inclusion of illustrations of lesions liable to be mistaken for leprosy. The book should be read and studied by all workers in tropical countries, with particular attention to Chapter XV on diagnosis and Chapters XVII and XVIII on treatment.

*Physicians Handbook.* By J. LARKENTIN, PH.D., M.D., and J. D. LANGE, M.S., M.D. Fourth Edition. Pp. 282. Chicago: University Medical Publishers. 1946. Price \$1.50.

The recent advances in medical knowledge have been included in this little book and so brought the fourth edition completely up-to-date. This handbook summarises clearly and concisely modern diagnostic procedures and other data and is a most useful little reference book for the physician.

*Laboratory Instructions in Biochemistry.* By I. S. KLEINER and L. B. DOTI. Second Edition. Pp. 245. London: Henry Kimpton. 1946. Price 30s. net.

Half the pages in this script are left blank for the purposes of student notes. The instructions given assume quite a fair knowledge of organic and physical chemistry; and a considerable amount of time available for the practice of biochemistry. Much of the text is devoted to descriptions of standard biochemical methods, and few of the qualitative tests are interpreted. The student must, therefore, have a good, sound biochemical textbook to hand which makes the "Laboratory Instructions" appear rather superfluous.

# BOOKS RECEIVED

- ACKERMAN, LAUREN V., M.D., and REGATO, JUAN A. DEL, M.D. Cancer : Diagnosis, Treatment and Prognosis . . . . . (Henry Kimpton, London) 100s. net.
- ALEXANDER, HARRY L., A.B., M.D. Synopsis of Allergy. Second Edition. (Henry Kimpton, London) 18s. net.
- BAMFORD, FRANK, B.S.C. Poisons : Their Isolation and Identification. Second Edition, revised by C. P. STEWART, M.S.C., PH.D. (J. & A. Churchill Ltd., London) 21s.
- BRUNSWIG, ALEXANDER, M.D. Radical Surgery in Advanced Abdominal Cancer . . . . . (The University of Chicago Press, Chicago, Illinois) 42s. net.
- CLENDENING, LOGAN, M.D., F.A.C.P., and HASHINGER, EDWARD H., M.D., F.A.C.P. Methods of Diagnosis . . . . . (Henry Kimpton, London) 63s. net.
- COLSON, JOHN H. C. The Rehabilitation of the Injured : Vol. II. Remedial Gymnastics . . . . . (Cassell & Co. Ltd., London) 30s.
- DAVIS, M. EDWARD, M.D., and CARMON, MABEL C., R.N. De Lee's Obstetrics for Nurses. Fourteenth Edition . . . . . (W. B. Saunders Co. Ltd., London) 15s. net.
- DAVES, BEN, D.S.C. (LOND.), A.R.C.S.C., D.I.C., F.L.S. Man and Animals: What They Eat and Why (A Manual of Nutrition). (Longmans, Green & Co., London) 7s. 6d. net.
- EWEN, JOHN H., F.R.C.P.E., D.P.M. Mental Health. (Edward Arnold & Co., London) 12s. 6d. net.
- FRANCIS, JOHN, B.S.C., M.R.C.V.S. Bovine Tuberculosis : Including a Contrast with Human Tuberculosis . . . . . (Staples Press Ltd., London) 25s.
- HENTSCHEL, C. C., M.S.C. (LOND.), and COOK, W. R. IVIMEY, B.S.C., PH.D. (LOND.). Biology for Medical Students. Fourth Edition. (Longmans, Green & Co., London) 25s. net.
- HEWER, EVELYN E., D.S.C. (LOND.). Textbook of Histology for Medical Students. Fourth Edition. (William Heinemann (Medical Books) Ltd., London) 21s. net.
- HIRSCH, EDWIN W., B.S., M.D. Sex Power in Marriage with Case Histories. (Research Publications of Chicago) \$3.00
- HOLMES, GEORGE W., M.D., and ROBBINS, LAURENCE L., M.D. Röntgen Interpretation. Seventh Edition . . . . . (Henry Kimpton, London) 35s. net.
- JERSILD, ARTHUR T., PH.D. Child Psychology. Third Edition. (Staples Press Ltd., London) 30s.
- KEEN, J. A., M.B. (LOND.), F.R.C.S. (ENG.). Ellis's Anatomy. (Stewart Printing Co. (Pty.) Ltd., Cape Town and John Murray, London) 42s. net.
- MEERING, A. B., S.R.N. A Handbook for Nursery Nurses. (Baillière, Tindall & Cox, London) 17s. 6d.
- Edited by MEIGS, JOE V., M.D., and STURGIS, SOMERS H., M.D. Progress in Gynaecology . . . . . (William Heinemann (Medical Books) Ltd., London) 35s. net.
- Edited by MEREDITH, W. J., M.S.C., F.INST.P. Radium Dosage: The Manchester System . . . . . (E. & S. Livingstone Ltd., Edinburgh) 15s. net.
- MILLIN, TERENCE, M.A., M.CH. (DUBL.), F.R.C.S., F.R.C.S.I. Retropubic Urinary Surgery . . . . . (E. & S. Livingstone Ltd., Edinburgh) 25s. net.
- MOORE, DOM THOMAS VERNER, O.S.B., M.D., PH.D. Personal Mental Hygiene. (William Heinemann (Medical Books) Ltd., London) 21s. net.
- QUIRING, DANIEL P., PH.D. The Head, Neck and Trunk. (Henry Kimpton, London) 14s. net.
- RIEBEN, W. K. Beiträge zur Kenntnis der Blutgerinnung. (Benno Schwabe & Co., Verlag, Basel) 9 F
- RUBIN, ELI H., M.D., F.A.C.P., F.C.C.P. Diseases of the Chest : With Emphasis on X-ray Diagnosis . . . . . (W. B. Saunders Company, London) 60s. net.
- SAMUELS, DR JULES. Endogeneous Endocrinotherapy including the Causal Cure of Cancer Compendium . . . . . (Holdert & Co., Amsterdam, Holland) —
- SCHWARTZ, LOUIS, M.D., TULIPAN, LOUIS, M.D., and PECK, SAMUEL M., B.S., M.D. Occupational Diseases of the Skin. Second Edition. (Henry Kimpton, London) 63s. net.
- STONE, KENNETH, D.M. (OXON.), M.R.C.P. Diseases of the Joints and Rheumatism . . . . . (William Heinemann (Medical Books) Ltd., London) 30s. net.
- Edited by TIDY, Major-General Sir HENRY LETHERY, K.B.E., M.D. Inter-Allied Conferences on War Medicine 1942-1945 (Staples Press Ltd., London) 50s. net.
- TREIGER, IRVING, J., M.D. Atlas of Cardiovascular Diseases. (Henry Kimpton, London) 50s. net.
- TREVES, Sir FREDERICK, Bart. Surgical Applied Anatomy. Eleventh Edition, revised by LAMBERT ROGERS . . . . . (Cassell & Co. Ltd., London) 20s.
- Edited by WAKELEY, Sir CECIL P. G., K.B.E., C.B. Hey Groves' Synopsis of Surgery. Thirteenth Edition . . . . . (John Wright & Sons Ltd., Bristol) 25s. net.
- Edited by WAKELY, Sir CECIL, K.B.E., C.B., D.S.C., F.R.C.S., etc. Modern Treatment Year Book 1947 . . . . . (The Medical Press, London) 15s.
- WIENER, KURT, M.D. Skin Manifestations of Internal Disorders (Dermadromes) . . . . . (Henry Kimpton, London) 63s. net.

# Edinburgh Medical Journal

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## PRODUCTION OF STREPTOMYCIN

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STREPTOMYCIN is an antibiotic of exceptional interest on account of its potential chemotherapeutic value in bacterial infections resistant to penicillin. It is active against the majority of pathogenic organisms, including Gram-positive, Gram-negative and acid-fast types; particular interest is being taken in its use against the various manifestations of tuberculosis. Clinical investigation now in progress (particularly in the U.S.A.) will indicate how far these hopes are to be fulfilled: see Hinshaw and Feldman.<sup>1</sup> The present paper describes investigations undertaken in Edinburgh with a view to producing streptomycin at a time when neither the drug itself nor even adequate details of the technique of preparation were available in this country. The latter were published during the course of our work.<sup>2,3,4</sup> The problems of large-scale production appear to be solved in the American factories, production now exceeding 200 Kg. per month,<sup>5</sup> but no details are available to indicate how the formidable technical difficulties were overcome. An account of our investigations may therefore be of value though we are well aware that the answers to some of our unsolved problems are now available in certain commercial laboratories.

### I. ASSAY OF STREPTOMYCIN

A suitable assay method was a prerequisite for this investigation and modifications of the tube-dilution and agar-diffusion or "cup"<sup>6</sup> methods employed in penicillin work were devised. We adopted Waksman's "S" unit, defined as "that amount of material which will inhibit the growth of a standard strain of *E. coli* in 1 ml. nutrient broth or other suitable medium."<sup>7</sup> Dr Waksman kindly provided a culture of his standard strain: this became available only when our investigations were nearly completed. Most of our results were obtained using a strain of *E. coli* selected arbitrarily from our stock of laboratory cultures. It proved, however, to have approximately

the same streptomycin-sensitivity as Dr Waksman's strain, and no adjustment of unitage was necessary on this score. We also employed *Staph. aureus*, "Oxford H strain" and, in a few cases, *Bacillus subtilis*. *Staph. aureus* was of value in the "cup" assay on account of its greater sensitivity to streptomycin resulting in larger zones of inhibition. In the dilution test, *Staph. aureus* consistently gave a bacteriostatic titre about four times greater than that of *E. coli* in parallel tests. Any divergence from this ratio would suggest the presence of antibiotics other than streptomycin.<sup>8</sup> A standard sample of streptomycin was necessary to control the bio-assays. We selected one of our early samples of streptomycin hydrochloride, of unknown purity, until the pure crystalline product was made available to us through the generosity of Dr W. H. Feldman of the University of Minnesota. In assaying this crystalline standard against Dr Waksman's test organism, we obtained only *one-third the titre usually cited by American workers*. All unitage figures quoted in this paper should therefore be multiplied by three for comparison with the American results. The source of this discrepancy is discussed below.

The *Agar-Diffusion* or "Cup" method does not require a sterile solution. We employed mainly *Staph. aureus* as test organism: *Bacillus subtilis* was tried but the edges of the zones were not sharp enough to be read accurately.

Petri dishes were poured with approximately 20 ml. of the following medium—Lab. lemco 1 per cent., peptone 1 per cent., sodium chloride 0.5 per cent., agar 2 per cent. pH was adjusted to pH 7.9: pH is a highly critical factor in streptomycin assay. When cool, the surface of the medium was inoculated with 2 ml. of a 1:1000 broth dilution of a sixteen to twenty-four hour broth culture of *Staph. aureus* "Oxford H strain," the excess inoculum removed and the plates dried in the usual way.<sup>6</sup> The inoculated plates were used within twenty-four hours though they could be stored at 0° C. for at least four days. Holes (usually five) were cut in the agar with a sterile  $\frac{1}{4}$  inch cork-borer, the bottoms of the holes sealed with a hot wire, and a few drops of the assay solutions (including a standard solution of known potency) placed in their respective holes. These holes replaced the usual porcelain cylinders of Heatley<sup>6</sup>: it was found that this technique gave larger zones of inhibition and more consistent results. (As in penicillin assay, the amount of test solution used is not critical). The plates were incubated for twenty-four hours at 37° C. and the zone diameters read to the nearest 0.5 mm. Fig. 1 is a typical calibration of a standard solution (streptomycin concentration plotted logarithmically).

A series of 19 assays of the standard sample, performed at intervals over a period of a month, gave an S.D. of 1.2 mm. for each reading, *i.e.* 0.6 mm. for an average of four readings. From Fig. 1 it is seen that this represents an accuracy of about 25 per cent. ( $P = 0.05$ ) for a group of four replicates. But though potentially accurate, the method was subject to frequent anomalies and irregularities, necessitating daily calibration of the standard and numerous replicates if

accuracy was to be maintained. The labour required was beyond our resources and we preferred the simpler tube-dilution assay.

The *Tube-Dilution* method is less accurate but more reliable since it involves fewer potentially variable factors. The necessity for using sterile solutions is a serious drawback, particularly as the Seitz filter-pads, although small, adsorbed streptomycin, necessitating rejection of the first 20 ml. of sterile filtrate. But sterilisation could be dispensed with altogether in many cases on account of the wide range of anti-bacterial activity of strong solutions of streptomycin. In assaying the culture filtrates of *Actinomyces griseus*, too, sterilisation was unnecessary since the organism grew too slowly to affect results. It was essential, when dispensing with sterilisation, to maintain a strict watch for contaminating organisms.

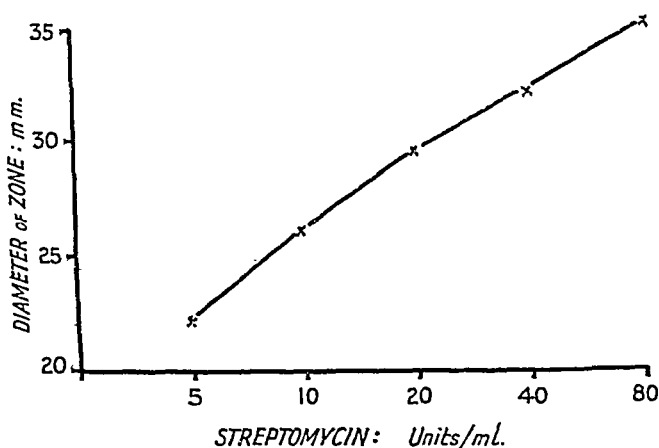


FIG. 1.—Assay of streptomycin by agar plate method.

Varying amounts of the material under test were incorporated by serial dilution in nutrient broth, pH 7.9 (0.3 ml. in  $3 \times \frac{1}{2}$  in. test tubes), each dilution being twice that of the previous tube. Half the contents of the last tube were removed, as is usual in such cases, but instead of being discarded was placed in a separate tube and incubated *without* inoculation with the test organism. This "discard control" served to reveal the presence of contaminating organisms, since the antibiotic in it was too far diluted to inhibit their growth. The usual "no streptomycin" control was also provided. All tubes except the "discard control" were inoculated with a 2 mm. platinum loopful of a 1:300 dilution of a sixteen to twenty-four hour broth culture of the test organism. Assays were usually performed in duplicate with *E. coli* and *Staph. aureus*. The tubes were incubated for twenty-four hours at 37° C. and the turbidities read visually. The final endpoint was obtained by stroke-inoculating on blood agar a loopful from the tubes above and below the endpoint, also control tube. Observation of the streaks after incubation (twenty-four hours at 37° C.) gave evidence of growth too weak to produce visible turbidity in the tubes, and distinguished bacteriostatic from bactericidal action by rough comparison of the number of colonies in the stroke-inoculum



with the number in a similar inoculum taken from the "no streptomycin" control *before* incubation. The presence of contaminants, if any, was also revealed. Each batch of tests was controlled by a similar titration of a standard preparation of known potency.

In assaying actively-growing fluid cultures, the sample was withdrawn aseptically, the bulk of the *Actinomyces griseus* removed by centrifugation, and the supernatant was assayed without sterile filtration. The slow growth of the few remaining organisms did not affect the endpoint of the assay.

The dilution of streptomycin, in most experiments, differed by a factor of two between adjacent tubes: *this must be borne in mind in the interpretation of assay results.* The use of graded dilutions with smaller differences between adjacent tubes increases the accuracy of the method, but such assays could be performed only on a few occasions during the present investigation. We feel that the use of the term "unit" to express the results of so inherently inaccurate a bio-assay procedure is undesirable, but have adopted it to conform with the practice of other workers. In repeated and carefully controlled experiments the dilution test, in our hands, assayed authentic (American) streptomycin hydrochloride at 260 units/mg. against the 700-800 units/mg. cited by American workers, though we were using the same strain of test organism. Our unitage should, therefore, be multiplied by three if our results are compared with theirs. Absolute bio-assay results may differ from one laboratory to another even with apparently identical techniques. We have no *precise* details of the American workers' dilution technique, though in at least two cases<sup>10, 11</sup> endpoints were read by turbidity only. Our practice of reading endpoints after stroke-inoculation on blood-agar of the relevant tubes permits the detection of growth insufficient to give visible turbidity, and hence tends to give lower titres.

## II. PRODUCTION OF STREPTOMYCIN IN SURFACE CULTURES

The technique described below does not depart essentially from that described by the American workers.

*Strain of Organism.*—Streptomycin is produced by *Actinomyces (Streptomyces) griseus*, isolated from soil by Schatz, Bougie and Waksman.<sup>12</sup> We obtained a strain, recommended as suitable by Dr Waksman, through the N.C.T.C. Stock Cultures were maintained on agar slopes (incubated at 26° C.) containing the usual inorganic salts with 1 per cent. glucose.

*Preparation of Inocula.*—A heavy inoculation with spores is essential for success. Five to ten day (26° C.) cultures were prepared on a medium similar to that used for the stock cultures with the addition of 0.05 per cent. asparagine. An agar flat in a 4 oz. bottle, giving a surface of 6 sq. ins., supplied inoculum for two Roux bottles. For inoculation the heavy crop of spores was detached from the surface of the agar with a sterile wire and suspended in 10 ml. saline.

*Medium.*—*Actinomyces griseus* grows readily on simple synthetic media but a growth factor or factors provided by meat extract or corn steep are essential for production of streptomycin in good yield.<sup>8</sup> We adopted a glucose-

broth medium (Lab. lemco 0.3 per cent.; peptone 0.5 per cent.; sodium chloride 0.5 per cent.; glucose 1 per cent.; tap water; pH 7.6). Addition of corn steep (1.2-2.4 per cent.), filtered or unfiltered, did not improve yield. Reduced yields were obtained when the 0.3 per cent. Lab. lemco was replaced by 1 per cent. meat extract; the claim<sup>4</sup> that yeast extract enhanced streptomycin production was not substantiated, addition of 1 per cent. of "Yeastrol" giving, on the contrary, a much lower yield.

*Culture.*—Roux bottles (50-100) of 800 ml. capacity containing 200 ml. of the medium (giving a layer 2 cm. deep when horizontal) were sterilised by three consecutive steamings and inoculated (see above). They were then incubated horizontally at 26° C., great care being taken to avoid disturbing the cultures, e.g. when withdrawing samples for assay. A thin but complete pellicle was formed in five days, the culture fluid now containing approximately 4 units/ml. A firm, fully developed surface growth had developed by seven to eight days with a titre of approximately 8 units/ml. Prolonging incubation up to ten to twelve days raised the titre to 16-32 units without any further increase in growth. In comparing this with the 100-200 units/ml. claimed by other workers,<sup>2,3,4</sup> the threefold difference in unitage should be borne in mind.\*

*Reflooding of Cultures.*—In some experiments the culture fluid was now withdrawn aseptically from beneath the mycelium, great care being taken to avoid damage to the latter, and fresh sterile medium added from 3-litre siphon flasks in which the medium, without glucose, had been autoclaved and the glucose added aseptically as a 50 per cent. solution. Streptomycin production was rapid in the recharged cultures, but the final yield was lower, 8-16 units/ml. being produced in three to four days. We failed, save in a single instance, to substantiate the claim that *higher* yields are obtained from recharged cultures.<sup>4</sup> The culture fluid could be again withdrawn and replaced, but after two or three rechargings the yields of streptomycin declined and the mycelium showed signs of deterioration quite apart from the inevitable mechanical damage. The mycelium was therefore discarded at this stage.

Culture bottles showing signs of contamination at any stage were discarded at once. A few bottles were selected at random from each batch and the culture fluid subcultured in broth, bullock-heart and blood-agar. Contaminants were seldom found except in recharged culture with senescent mycelia.

The extraction and purification of the streptomycin is described in Section IV.

### III. PRODUCTION OF STREPTOMYCIN IN AERATION CULTURES

The surface-culture method, described above, necessitates considerable expenditure of labour in preparing large quantities of inoculum and numerous cultures. This is overcome by the use of fewer culture vessels of larger capacity: in this case, forced aeration is essential and we have the "deep culture" method now universal in the large-scale production of penicillin. A further advantage (less marked, however, with streptomycin than penicillin) is that conditions for growth are more favourable and production of the antibiotic more

\* In this connection it should be noted that the strain of *A. griseus* used in this investigation (although the most active available at the time) may not produce as much streptomycin as the strains used by some of the American workers.

rapid, with further economy of plant and space. The practical difficulties are perhaps even greater than with penicillin. Sterilisation of a relatively large bulk of medium (2 litres per culture-bottle in our experiments) requires prolonged autoclaving with serious risk of damage to the medium unless a continuous-flow steriliser is available. Such a steriliser was not available. The maintenance of sterility during several days' rapid aeration is an even more difficult problem. A single contaminant can spoil far more material than in the smaller units of the surface-culture method, and may spread to other culture-vessels through the aeration system. In penicillin production the problem is much simplified by working at  $pH$  as low as 4; this is not permissible with streptomycin. Our work was performed under ordinary laboratory conditions and without special equipment: we are very doubtful whether consistent success can be achieved without specially designed apparatus preferably in rooms used exclusively for this work. The strictest bacteriological control must be maintained *at all stages*: an examination for contaminants at the end of each experiment is not sufficient, as serious error may arise through a contaminant obtaining access and multiplying, but being destroyed by the rising titre of streptomycin. We considered the addition of penicillin to the medium as a means of reducing the risk of contamination and in two batches introduced 0.5 units/ml. into some of the culture vessels. This is well below the bacteriostatic level for *Actinomyces griseus* which is fairly resistant to penicillin. Unsatisfactory "no penicillin" controls in these experiments unfortunately prevented adequate assessment of the results and we were unable to investigate this point further. The suggestion may, however, prove of practical value.

The most serious difficulty was the operation of unknown factors which reduced or suppressed the formation of streptomycin without visibly retarding growth. We sometimes failed to obtain reproducible results even from replicate culture-vessels. Consistently successful results will not be obtained with the aerated-culture method until these factors are elucidated and controlled. We lacked the resources and time for completion of this investigation and our yields never approached those consistently achieved by the surface-culture method, where these factors presumably do not operate. Our strain of organism, too, chosen for the surface-culture method, may not have been the most suitable for deep cultures.

*Apparatus* (Fig. 2).—Compressed air was passed through a regulator (A)<sup>13</sup> stabilising the flow at 4.7 litres/minute, a flow-meter (B) and two 15×1 in. tubes (C) loosely packed with sterile cotton-wool. The air, now sterile, was passed through a wash-bottle (D) immersed in the incubator tank (E). This prevented evaporation of the culture fluid by saturating the air at the incubation temperature. The wash-bottle and culture-vessels (F) were fitted with metal screw-cap fittings of the type used for sterile filtrations. The four culture-vessels (only one is shown in the diagram) were immersed in a tank maintained

at 26° C. Each had a capacity of 4 litres and contained 2 l. of medium. They were connected in series; this increased the risk of a contaminant spreading from one vessel to the next, but parallel arrangement would have necessitated the sterilisation of an even larger volume of air. The culture-vessels carried three-way fittings, the third (top) outlet (G) being closed by a rubber cap which could be removed for withdrawing samples (see below). The air from the last wash-bottle was bubbled through phenol (J) to prevent entry of contaminants: the empty wash-bottle (H) served as a trap to avoid the risk of phenol being sucked back into the culture vessels.

*Inoculum* was prepared as for the surface-cultures: the entire crop from one 4 oz. agar flat (area 6 sq. ins.) was used for each culture-vessel.

*Medium*.—Same as for the surface-cultures, but the concentration of glucose was varied:—3.4 per cent. appeared to be optimal. The medium, without glucose, was sterilised in the culture-vessels by autoclaving (15 lbs. for forty minutes) and the glucose added as a sterile 50 per cent. solution.

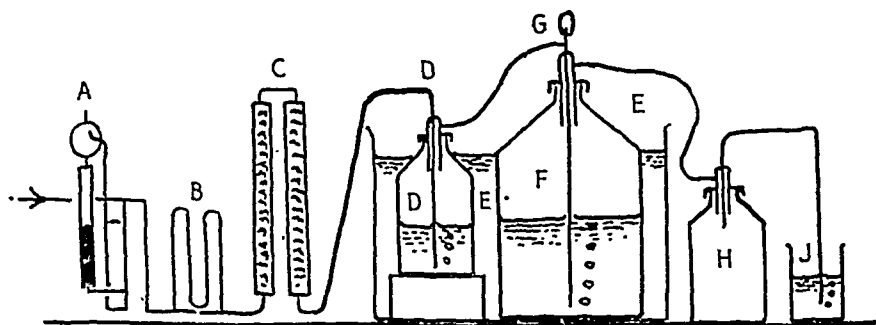


FIG. 2.—Preparation of streptomycin in aerated cultures.

A, Air pressure regulator; B, Air-flow meter; C, Sterile cotton-wool tubes; D, Wash-bottle for saturating air; E, Thermostat tank (26° C.); F, Culture vessel(s); G, Removable cap for taking samples from culture vessel; H, Trap; J, Outlet immersed in jar of aqueous phenol.

Lard oil (0.025 per cent. sterilised for one hour at 150° C.) was added to retard frothing.

*Technique*.—The cotton-wool tubes (C, Fig. 2), the wash-bottles D and H and the various connections and fittings were sterilised: the sterile culture-vessels containing the medium were inoculated and the screw fittings inserted. The apparatus was assembled with aseptic precautions and the culture-vessels and wash-bottle D inserted in the 26° C. thermostat tank. Extremely vigorous aeration was now applied with an air-flow of approximately 5 litres/minute.

Samples were withdrawn every one to two days for antibiotic assay and examination for contaminants. Special pipettes (Fig. 3A) drawn from  $\frac{1}{8}$  in. tubing were used: the stem was 1.2 mm. diameter, flexible and long enough to reach to the bottom of the culture-vessel. A sheath (B) and 8×1 in. test-tube (C) protected the fragile pipette during sterilisation. Samples were taken by stopping the air-stream (care necessary to avoid sucking-back), removing and discarding cap G (Fig. 2) from the culture-vessel, withdrawing 5-10 ml. culture-fluid with a pipette inserted down the narrow inlet tube, and replacing G by a fresh sterile cap. The sample was then assayed for streptomycin and examined for contaminating organisms thus: (i) a portion was

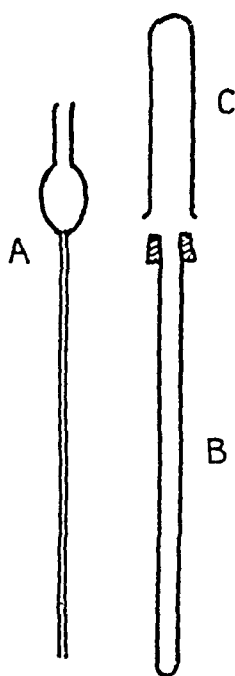


FIG. 3.—Sampling pipette (A) and protective sheath (B, C).

centrifuged, the sedimented organism washed with acetone to remove fatty substances which prevented satisfactory staining, and a Gram-stained film prepared; (ii) a few drops were subcultured in broth and in bullock heart medium and examined after incubating at  $37^{\circ}\text{C}$ . for twenty-four hours; (iii) a plate-culture on blood-agar prepared and incubated at  $37^{\circ}\text{C}$ . for twenty-four hours. Duplicates of (ii) and (iii) were prepared in some cases and incubated at  $26^{\circ}\text{C}$ . Bacteriological examination was complicated by the extreme pleomorphism of both *Actinomyces griseus* and the aerobic sporing organisms ("*B. anthracoides*") which were the most troublesome contaminants: the former often broke up, under the vigorous aeration, into bacillus-like fragments, or formed oval Gram-positive spores: the latter were irregular in their Gram reaction and sometimes formed chains or even apparently continuous filaments.

Maximal growth was obtained in two days, maximal streptomycin titre (4.8 units/ml.) in four to six days.  $\text{pH}$  did not alter significantly despite the metabolism of most of the glucose. Contaminated cultures were rejected (in any case, presence of a contaminant usually prevented streptomycin production) and at the end of the experiment the mycelium was removed by filtration. Yields, as noted above, were not constant and, contrary to experience with the surface-cultures, did not appear to be correlated with growth.

#### IV. EXTRACTION OF STREPTOMYCIN

Streptomycin is an organic base,  $\text{C}_{21}\text{H}_{39}\text{N}_7\text{O}_{12}$ .<sup>\*</sup> It is adsorbed on charcoal at neutral but not at acid  $\text{pH}$ : this is the basis of our extraction procedure, which follows closely that of Carter *et al.*<sup>2</sup> Further purification is effected by chromatography on activated alumina.<sup>2</sup> The same technique was applied to surface and deep culture filtrates.

The filtrate from 40 surface-culture bottles (7.4 litres,  $\text{pH}$  7.8, 50 units/ml., total 370,000 units) was acidified to  $\text{pH}$  2 by addition of concentrated  $\text{HCl}$  (36.3 ml.); 37 gm. (*i.e.* 0.5 per cent.) of charcoal (Farnell's No. 14) was added and the mixture was stirred mechanically for ten minutes. The charcoal was filtered off and discarded, the small amount of streptomycin it contained being not worth recovery. The pale yellow filtrate ( $\text{pH}$  2.1) was neutralised ( $\text{pH}$  7.0–7.5) with *N*  $\text{KOH}$  (290 ml.) and the streptomycin adsorbed by stirring mechanically for ten minutes with 74 gm. (1 per cent.) charcoal; the  $\text{pH}$  fell during stirring to 6.0 and was restored with more *N*  $\text{KOH}$  (45 ml.). A further ten minutes stirring now produced no fall in  $\text{pH}$ ; the charcoal was

\* The structure of streptomycin has been elucidated<sup>14</sup> since this paper was written.

filtered off, and the clear, almost colourless filtrate discarded. Certain pigmented impurities were eluted from the charcoal by stirring for five minutes in 300 ml. ethanol, and for five minutes in 300 ml. methanol: these extracts were discarded.

The streptomycin was now eluted from the charcoal by stirring mechanically for ten minutes with methanol (430 ml.) to which HCl was added so that the mixture was 0.1 *N*. The treatment was repeated and the extracted charcoal discarded. The combined eluates were run slowly into 4 vols. ether with stirring: the flocculent precipitate of crude streptomycin hydrochloride settled in a few minutes and the supernatant was decanted off. The precipitate was dissolved in methanol and reprecipitated with ether, filtered, washed on the filter with a few ml. of ether, and *rapidly* transferred to a vacuum desiccator. Yield 2.60 gm. (350 mg./litre culture fluid), fine, non-hygroscopic powder, 64 units/mg. streptomycin: total 166,000 units, representing 46 per cent. recovery.

Activated alumina for chromatographic purification of the crude streptomycin was prepared by treating 200 gm. Peter Spence Type H alumina with sufficient 50 per cent. sulphuric acid (200-250 ml.) to give a slurry, standing for thirty minutes and washing 10 times with 2 litres distilled water. The final washings contained only a trace of sulphate. The alumina was transferred as a slurry to two tubes, 25 mm. diameter, to form columns approximately 25 cm. long. The columns were washed with 100 ml. water followed by 200 ml. 80 per cent. methanol prior to use. A typical purification is now described: crude streptomycin hydrochloride (2.0 gm., 100 units/mg., total 200,000 units) was dissolved in 80 per cent. methanol (18 ml.) and neutralised to pH 6.3 (bromocresol purple) by addition of 2 *N* lithium hydroxide in 80 per cent. methanol (2.1 ml.). A heavy flocculent precipitate of inactive material was removed by centrifugation. The solution was poured on to one of the alumina columns, which was developed with 80 per cent. methanol and fractions collected (table I).

TABLE I

Fraction.	Volume.	B/Static Titre.	Total Units.	Sakaguchi Reaction.	N mg. ml.
1	50 ml.	...	...	0	...
2	25 ml.	1:25	600	0	...
3	25 ml.	1:25	600	++	0.30
4	25 ml.	1:5120	130,000	++++	1.52
5	25 ml.	1:1280	30,000	+++	0.76
6	50 ml.	1:160	8,000	++	0.38
7	75 ml.	1:80	6,000	+	0.13
8	100 ml.	1:32	3,200	++	0.07

The guanidine groups in streptomycin are responsible for the Sakaguchi reaction: fraction 3, however, contains Sakaguchi-positive material which is biologically inactive. In some batches this was more sharply separated from the streptomycin-containing fractions. Four-fifths of the streptomycin appears in fractions 3 and 4: in view of the errors of assay this figure must be only approximate, but is fairly representative of our experience. These two fractions were combined, the methanol removed *in vacuo*, and the resulting aqueous solution was freeze-dried. Yield 0.40 gm., 250 units/mg.: *i.e.* 100,000 units: on our unitage, this represents nearly pure streptomycin hydrochloride.

*Preparation of the Crystalline Helianthate.*<sup>15</sup>—Chromatographically purified streptomycin hydrochloride (1.4 gm., 250 units/mg.) was dissolved in 25 ml. methanol at 55° C. and 1.1 gm. helianthine in 70 ml. water at 75° C. added with stirring. The precipitate was centrifuged after allowing to stand at room temperature for twenty-four hours, and recrystallised from 300 ml. of hot 33 per cent. methanol, the fine crystals being filtered off only with difficulty. The product was washed successively with 100 ml. water and 25 ml. each of isopropanol, acetone and ether, and dried *in vacuo*. Yield 0.76 gm., 80 units/mg.: *i.e.* approximately one-third of the potency of the standard crystalline (American) streptomycin hydrochloride: calculated on the basis of streptomycin content, our product was as active as this standard material within the limit of error of assay.

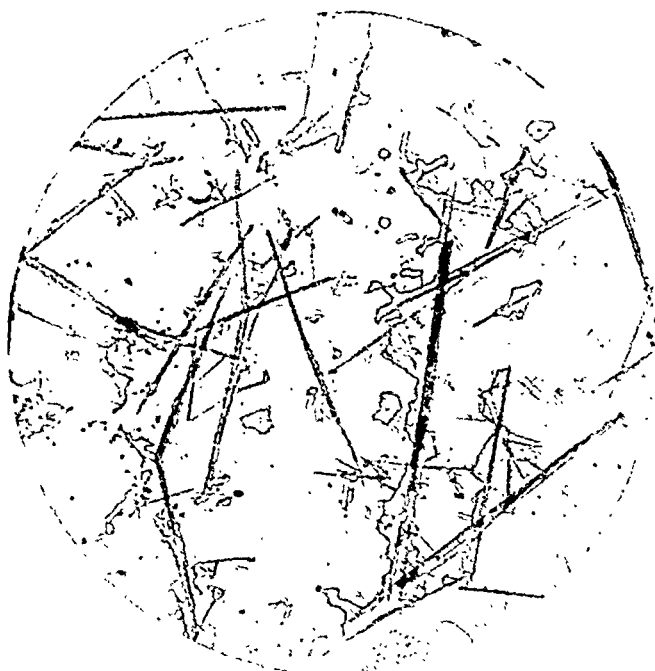


FIG. 4.—Streptomycin helianthate.  $\times 100$ .

Analysis (Dr G. Weiler, Oxford): C, 47.5 per cent.; H, 6.12 per cent.; N, 14.5 per cent.; S, 6.52 per cent. After further recrystallisation from hot water, C, 47.1 per cent.; H, 6.00 per cent.; N, 15.3 per cent.; S, 6.28 per cent. Calculated for  $C_{21}H_{39}N_7O_{12}$  ( $C_{14}H_{15}N_3O_3S$ )<sub>3</sub>; C, 50.52 per cent.; H, 5.65 per cent.; N, 14.97 per cent.; S, 6.42 per cent. Long narrow plates, deep orange: decompose without melting (Fig. 4).

#### SUMMARY

The production of streptomycin in both surface and deep aerated cultures of *Actinomyces griseus* is described, with details of the method of extraction, purification and assay.

Streptomycin was assayed by the tube-dilution method, and by the agar-diffusion methods. The former method was preferred as it was more reliable and less time-consuming.

Streptomycin was produced in surface cultures on a glucose-meat-extract broth. The crude culture fluids contained about 30 units/ml. our unit being equivalent to 3 units of the American workers. The practicability of the reflooding of cultures for streptomycin production has been confirmed.

Apparatus and technique are described for the production of streptomycin in deep cultures with forced aeration. Considerable difficulty was found in excluding contaminating organisms, and variations in yield were produced by unknown factors.

Streptomycin was extracted by adsorption on charcoal at neutral pH and elution with acid methanol, purified by chromatography on acid-washed alumina and crystallised as the helianthate.

This work has occasioned demands which weigh rather heavily on the resources of a university department. We wish to express our gratitude to Professor T. J. Mackie, C.B.E., for providing the facilities and for his most helpful interest, encouragement and advice. Our thanks are also due to Miss M. E. Davies for her help in the bacteriological examination of cultures and to Miss J. Wallace for her invaluable technical assistance.

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## PHYSICAL AND CHEMICAL FACTORS CONCERNED IN HÆMOLYSIS

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THE phenomenon of hæmolysis of erythrocytes in hypotonic solution was first studied by Hamburger about sixty years ago. Since then, a great mass of literature has appeared on the subject of the permeability of erythrocytes and other animal cells, while the field around the original problem of osmotic fragility has been left comparatively untouched. We are still without definite answers to such questions as the structure of the red cell, the events which occur during the liberation of hæmoglobin from it, the actual factor or factors which determine whether or not an erythrocyte shall hæmolyse, and many other interesting problems. Nor have the pathological variations in osmotic fragility been fully investigated. It is true that many observations have been made on the decreased resistance of erythrocytes in hæmolytic anæmia, and on the increased resistance in obstructive jaundice, but apart from the observation that the resistance is altered, no profitable investigation of these variations has so far been undertaken, and the problem of alteration of resistance in other diseases has scarcely been touched.

The red cell fragility test as described in textbooks and as practised clinically, is sufficient to give an indication of increased, normal, or decreased resistance, but it is by no means a quantitative test although standard solutions of salt are employed. It is, indeed, merely a qualitative test, for it is impossible to decide, with any degree of precision, where hæmolysis begins, or where it ends. In order to make the test quantitative, and so enhance its value, it is necessary to determine accurately, the degree of hæmolysis in a large series of saline concentrations, and to study the curve obtained by plotting the degree of hæmolysis against the corresponding concentration of salt (the "hæmolysis curve"). This has been done by several workers using two quite different methods. In the first, the percentage of un-hæmolysed cells in each saline concentration is determined by the usual hæmatological methods, *e.g.* Whitby and Hynes (1935); in the second, the percentage of hæmoglobin liberated into the hæmolysing solution has been determined by the amount of colour which it produces, *e.g.* Dacie and Vaughan (1938). Both methods give essentially the same results in the form of a sigmoid curve, but whereas the cell-counting method is slow and laborious, and, in tubes with extensive hæmolysis, difficult and inaccurate owing to the presence of "ghost" cells, the method based upon the determination of the

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liberated hæmoglobin is rapid, highly reproducible, and accurate at any degree of hæmolysis.

The principles of these methods are open to objection. Both are based on the assumption that every red cell which hæmolyses liberates the whole of its hæmoglobin, and that every cell which does not hæmolyse, retains the whole of its hæmoglobin: in other words, they assume that the "all-or-none" law is obeyed in osmotic hæmolysis. The second method (based on the determination of the liberated hæmoglobin) makes the further supposition that every cell has the same hæmoglobin content; an assumption which is probably very near the truth in the case of blood from normal, healthy individuals; an assumption which possibly holds in the majority of pathological conditions; but an assumption which is certainly false in cases of mixed microcytic-macrocytic anæmias. This latter complication will affect the course of hæmolysis only if the two types of cells (microcytic and macrocytic) hæmolyse to different extents in the various saline dilutions.

Another factor which must be taken into consideration is the increase in osmotic pressure of the hæmolysing solution due to the solutes of the plasma when whole blood is added to the saline. In the study of the hæmolysis of normal blood, this factor has at least the virtue of being relatively constant and can therefore be neglected provided that the dilution of the blood in the hæmolysing solution is kept constant. In the blood from an anæmic person, the error introduced by its neglect may be considerable. The problem is discussed at length by Dacie and Vaughan (1938).

These considerations are by no means the only ones which may have an effect upon the degree of hæmolysis (real or apparent) in any given hypotonic solution. The nature of the solute in the hæmolysing system has to be considered. The vast majority of studies in osmotic hæmolysis have employed sodium chloride solutions of varying concentration. Occasionally, other electrolytes, or non-electrolytes such as urea, have been used. In these cases, the nature of the solute requires careful examination. If the solute be an electrolyte, the ions may have specific effects upon the red cell—hydrogen and hydroxyl ions being the most important in this respect. With non-electrolytes, the nature of the various active groups in the molecule may play a decisive part in causing hæmolysis irrespective of the concentration of the solute, *e.g.* small molecular alcohols such as ethyl alcohol bring about rapid and complete hæmolysis.

The oxygen tension of the blood, and the  $pH$  and temperature of the hæmolysing system have been shown by Jacobs and Parpart (1931) all to have effects upon the degree of hæmolysis, and Whitby and Hynes (1935) have demonstrated that there are such great differences between the degrees of hæmolysis shown by venous, capillary, and arterial blood, that they advocate the full oxygenation in a tonometer, of all samples of blood prior to the determination of the hæmolysis

curve. Variation of  $pH$  is to be avoided in all such biological procedures, but most experimenters have relied on the buffering capacity of the added plasma alone to ensure a constant  $pH$ . That a greater degree of buffering capacity is desirable, was claimed by Simmel (1923) who introduced a hæmolysing solution containing, amongst other salts, acid sodium phosphate and sodium bicarbonate. The advantage of having a buffering system incorporated in such a complicated hæmolysing solution, is counterbalanced by the difficulty (or impossibility) of calculating the osmotic pressure of such a mixture, and furthermore, the buffering capacity of Simmel's solution is strictly limited.

Temperature also has its effect upon the degree of hæmolysis. The extremes of temperature bring about extensive hæmolysis even when the cells are suspended in physiological saline. Sufficient control of temperature can be attained by allowing not more than a variation of  $1^{\circ} C.$  : at  $18-20^{\circ} C.$ , the temperature coefficient is small.

The scientific study of the behaviour of any biological material demands that all influencing factors (both external and internal) shall be known and controlled. These factors may be not only physical factors such as those mentioned above, but will also include biological factors. That the inherent properties of each erythrocyte influence the behaviour of that cell towards a hæmolysing solution, cannot be reasonably doubted. The variations in behaviour of the red cells in cases of hæmolytic anæmia and obstructive jaundice have already been noted, and it has been shown by Stephens (1940) that reticulocytes are more resistant to osmotic hæmolysis than are mature cells. Variation even in the normal population of cells is therefore another factor.

During the process of venepuncture the negative pressure applied in the syringe is sufficient to bring about a small loss of carbon dioxide and a change in  $pH$ , unless the blood be withdrawn under oil. After withdrawal, certain changes begin to occur at once. There is a redistribution of ions between cells and plasma, hexose breaks down to lactic acid, phosphoric acid esters begin to hydrolyse, and so on. Many of these reactions are known to be catalysed by enzymes. Any or all of them may influence the hæmolysis of erythrocytes, and indeed it will be shown that such alterations have a profound effect upon the degree of hæmolysis.

Lastly, among known factors, one has to consider the effects of the addition of anticoagulants. The anticoagulant most commonly used in work of this type is the mixture of the oxalates of potassium and ammonium in the amounts recommended by Heller and Paul (1934). This mixture has the minimum effect on the size and shape of the cells and is the one in general use in hæmatology. The precipitated calcium oxalate plays no further part in any reaction since it forms a separate, highly insoluble, phase. But the calcium ion removed is replaced by an equivalent amount of potassium and ammonium ion, and any excess oxalate contributes to the osmotic pressure of the

hæmolysing solution. These effects are small since the amount of anticoagulant is reduced to a minimum, and they can probably be disregarded with safety.

Little need be said concerning the internal structure of the mature erythrocyte. Most authors state, or imply, that the cell is surrounded by some membrane whether this be a corporeal structure or simply a liquid-liquid interface. Some claim to have separated this membrane from whole blood and to have obtained it in the form of a lipoid-protein complex sometimes known as "stromatin" with definite chemical and physical properties. A small part of the hæmoglobin of blood always remains attached to the stromatin: when blood is completely hæmolysed by diluting it 20-25 times with water, the "ghost cells" which centrifuge down are always coloured and the pigment cannot be removed by repeated washing with water. Such stromatin always gives a strong benzidine reaction. Some authors believe that a small part of the hæmoglobin is firmly attached to the stromatin network and cannot be removed by physical methods. The writer would draw attention to two points in this connection, (i) that the deposit of stromatin never contains any structure which can be recognised microscopically as a "ghost cell," and (ii) that the euglobulin of serum or plasma is precipitated under identical conditions.

An essential preliminary to hæmolysis by hypotonic solutions is the assumption of a spherical form by the erythrocyte: Jacobs (1930), Ponder and Saslow (1931), Ponder (1934), Guest and Wing (1942), etc. This is in accordance with the fact that fluid moves across a semipermeable membrane from the region of lower, to the region of higher, osmotic pressure. What happens next is a mystery. The older theory, that the stretched membrane simply bursts, is no longer generally held. This much is certain, that the erythrocyte quite suddenly loses the whole of its hæmoglobin and becomes a ghost cell, but what factors determine the moment at which the hæmoglobin will escape, are not known. Nor do we understand why, in say, 0.410 per cent. saline, half of the cells should hæmolyse, while the other half do not. The explanation, "individual variation" merely postpones the discovery of the cause or causes.

#### EXPERIMENTAL METHODS

Human blood obtained by venepuncture without the use of oil, has been used in all the following work.

In the majority of experiments, hypotonic solutions of sodium chloride have been used as the hæmolysing system. 9.50 c.c. of saline is pipetted into a specially cleaned, dry tube. 0.50 c.c. of oxalated blood is then added, and the tube is closed by a rubber stopper; the contents are well mixed, and allowed to stand for a definite period (usually one or two hours). In these experiments, the tubes stood

in an incubator are room temperature, which controlled the temperature to within  $0.2^{\circ}\text{C}$ . After standing, the contents of the tube are again mixed and then centrifuged. The clear supernatant is at once transferred to a second clean, dry tube.

Hæmoglobin is determined by the alkaline hæmatin method of Clegg and King (1942) which is by far the most accurate and reproducible method of many which have been tried. 2.00 c.c. of the supernatant fluid is transferred to a tube marked at 10.00 c.c. Approximately 8 c.c. of N/10 sodium hydroxide is added, and the tube is then heated in a boiling-water bath for four minutes. It is cooled in running water, made up to 10.00 c.c., and the intensity of the colour determined by a Spekker photoelectric absorptiometer using a green filter, and taking distilled water as the standard.

A second tube in which 0.50 c.c. of blood is added to 9.50 c.c. of 0.900 per cent. (or sometimes, 0.700 per cent.) sodium chloride, is treated in the same way. The reading obtained is taken as the "blank": in normal blood, no hæmolysis ever occurs in these concentrations, but this blank always shows some slight degree of light absorption due to the presence of (i) proteins and also, possibly, lipoids derived from the plasma, and (ii) the pigments normally circulating in the plasma. The blank so obtained is used to correct all other figures.

A third tube, in which 0.50 c.c. of blood is added to 9.50 c.c. of distilled water, is treated in the same way. Hæmolysis is rapid and complete, and the absorptiometer reading (corrected for blank) is taken to represent 100 per cent. hæmolysis. The amount of hæmoglobin remaining attached to the stromatin is a negligible fraction of 1 per cent.

If the absorptiometer readings in these three tubes are  $a$ ,  $b$ , and  $c$  respectively, then the percentage hæmolysis in the first tube (containing hypotonic saline) is taken to be

$$\frac{(a-b) \times 100}{(c-b)} \text{ per cent.}$$

This calculation is justified on the grounds that the extent of absorption of light is directly proportional to the concentration of alkaline hæmatin over the ranges of alkaline hæmatin concentration which may be encountered. Crystalline hæmatin ( $\text{Fe} = 8.48$  per cent.: calculated for  $\text{C}_{34}\text{H}_{32}\text{O}_4\text{N}_4\text{FeCl}$ ,  $\text{Fe} = 8.57$  per cent.) has been prepared by the method of Delory (1943), and has been used to standardise this calculation.

The percentage hæmolysis figures so obtained are independent of the red cell count, except in so far as a diminished cell count implies an increased percentage of plasma in the added blood, and this in turn will affect the osmotic pressure of the hæmolysing system. This comes into play only when dealing with anæmic blood and does not affect the following experiments.

All  $pH$  determinations were carried out with either the Beckmann glass-electrode  $pH$ -meter, or the Cambridge (Marconi) glass-electrode  $pH$ -meter.

### EXPERIMENTAL

*The "All-or-None" Law in Hæmolysis.*—For reasons already mentioned, it is of primary importance to determine whether "56 per cent. hæmolysis" means that 56 per cent. of the cells have liberated the whole of their hæmoglobin, or that each cell has liberated 56 per cent. of its hæmoglobin, or that some cells have liberated all, and others part, of their hæmoglobin giving an apparent value of 56 per cent. hæmolysis.

This problem can be investigated as follows: a specimen of normal blood is distributed in a series of saline concentrations giving different degrees of hæmolysis. After standing for two hours, the mixture is centrifuged and the supernatant is removed for determination of the degree of hæmolysis. It is immediately replaced by an equal volume of 0.900 per cent. sodium chloride which stops any further tendency to hæmolysis. The unhæmolysed cells are shaken up in this medium, centrifuged, and washed twice with normal saline to remove all extracellular hæmoglobin. The washed cells are finally suspended in exactly 10.00 c.c. of normal saline. In this suspension we determine (i) the total hæmoglobin by the method of Clegg and King, and (ii) the total number of red blood cells present, by suitable dilution and the use of a hæmocytometer. From these figures, the mean corpuscular hæmoglobin (M.C.H.) is calculated, or (taking the M.C.H. of the normal as 29.5 micromicrograms) the colour index of the unhæmolysed cells in each tube is determined.

TABLE I

*The Mean Corpuscular Hæmoglobin and Colour Index of the Unhæmolysed Cells at Varying Degrees of Hæmolysis*

	Blood Specimen No. 1.				Blood Specimen No. 2.				
NaCl concentration (per cent.).	0.900	0.425	0.410	0.395	0.900	0.425	0.410	0.395	0.380
percentage hæmolysis	0.0	6.0	14.6	43.6	0.0	22.8	46.0	70.0	81.8
total cell Hb (mgms.)	74.5	68.5	62.5	39.2	77.5	58.5	37.7	23.1	12.6
total cell count ( $\times 10^9$ ).	2.72	2.26	2.14	1.19	2.37	1.90	1.08	0.74	0.41
M.C.H. (micromicrograms).	27.4	30.3	29.2	33.0	32.7	30.8	34.8	31.3	30.5
Colour Index	0.93	1.03	0.99	1.12	1.11	1.04	1.18	1.06	1.03

The results in two such experiments are shown in Table I, and it will be seen from these figures that the colour index remains remarkably constant. If each cell liberated only part of its hæmoglobin, a fall in the colour index would be inevitable, and the lowest values for the index would be shown in the tubes with the greatest degree of hæmolysis. Since there is no indication of such a fall, one

may safely assume that the "all-or-none" law is obeyed. It is interesting to note in passing that the presence of "ghost" cells does not interfere with the hæmocytometer counts unless one is dealing with a specimen which has been hæmolysed to the extent of 80 per cent. or more. Up to this point, "ghost" cells are very rarely seen.

In preliminary experiments, it became evident that two "time factors" were of importance in determining the extent to which a specimen of blood would hæmolyse in a given saline concentration. These are (i) the time elapsing between the withdrawal of the blood and its introduction into saline, and (ii) the length of time that the cells are allowed to stand in contact with the hæmolysing system.

If a specimen of venous blood is allowed to remain in a closed tube which is opened at intervals to allow samples to be removed, it is found that successive specimens show a progressively diminishing degree of hæmolysis in a given concentration of hypotonic saline. The change is considerable. In one experiment, it was found that the percentage hæmolysis two minutes after withdrawal was 75 per cent. in 0.410 per cent. saline; after standing for nine hours, this value has dropped to 30 per cent. in the same concentration of saline. Samples taken at intermediate time intervals showed corresponding changes. The magnitude of this change depends upon the concentration of the saline, and is, of course, maximal when using the concentration producing 50 per cent. hæmolysis. Consideration of these figures led, by a rather roundabout route, to a phenomenon already described in the literature. Whitby and Hynes have observed the difference in fragility between the erythrocytes of venous and arterial blood, and these authors conclude that the difference is due to the more perfect oxygenation of the latter. During such an experiment as that described above, the blood visibly became more oxygenated, and it was therefore concluded that this alteration in hæmolysis, and the changes in fragility on oxygenation as described by Whitby and Hynes, were one and the same thing.

The effect of oxygenation on the fragility of red cells can readily be demonstrated by keeping part of a specimen of blood in the "venous" state, and exposing the rest to an atmosphere of pure oxygen for fifteen minutes in a tonometer. Both are then distributed in hypotonic saline and the percentage hæmolysis is determined in each.

TABLE II

*Showing the Effect of Oxygenation on the Fragility of Erythrocytes from Seven Different Samples of Blood*

NaCl concentration (per cent.)	Percentage Hæmolysis						
	0.410	0.410	0.410	0.395	0.395	0.395	0.395
Venous blood . . . . .	56	48	75	42	80	72	42
Oxygenated blood . . . . .	9	14	21	9	16	27	6

This fall in percentage hæmolysis after oxygenation would obviously have a profound effect on any hæmolysis curve. Why such a simple process should produce such a striking alteration in fragility has never been explained. Before discussing it further, it would be well to consider the other "time factor" which was mentioned above.

Partial hæmolysis by hypotonic saline is not an instantaneous process. The majority of erythrocytes which are destined to hæmolyse, do so very rapidly, but the process does not stop at that point. The longer the cells are allowed to stand in contact with the hæmolysing system, the greater is the chance of any individual (unhæmolysed) cell undergoing the process of hæmolysis. This can be shown by distributing a sample of blood into several tubes of saline of the same concentration, allowing the tubes to stand for varying times, and then determining the percentage hæmolysis in each.

TABLE III

*Showing the Increase in Hæmolysis which Occurs when Three Different Samples of Blood are Allowed to Stand in Contact with Hypotonic Saline*

Time (in hours) . .	Percentage Hæmolysis.					
	$\frac{1}{2}$	2	3	4	5	8
1. Venous blood . .	35.4	38.6	40.4	47.4	...	...
2. Venous blood . .	47.5	49.1	51.1	...	55.5	57.0
3. Oxygenated blood .	14.3	14.9	14.3	...	16.1	18.4

There is a gradual increase in percentage hæmolysis the longer the blood stands in contact with the saline, and this change occurs with both venous and oxygenated blood. By similar experiments, it can be shown that the increase does not occur in higher concentrations of saline where there is no hæmolysis, nor in distilled water or very low concentrations of saline where hæmolysis is rapid and complete. It cannot be associated with the process of progressive oxygenation which would tend to decrease the fragility, and its cause is unknown unless it be that different members of the cell population take different times to reach that critical point at which they begin to hæmolyse. These changes in fragility are relatively small, and can be controlled completely in a study of hæmolysis by keeping this particular "time factor" constant—a precaution which any experimenter would instinctively take.

Returning to the effect of oxygenation on fragility, it is known that venous blood still has about 65 per cent. of its hæmoglobin in the form of oxyhæmoglobin, and only about 35 per cent. in the reduced state. If oxygenation of the reduced hæmoglobin produces a dramatic increase in the osmotic resistance of the cells, one would expect, *a priori*, that de-oxygenation of the remaining oxyhæmoglobin



(e.g. by exposure to a vacuum) would cause an equally dramatic decrease in the resistance of the cells. That this is not the case, is shown by the figures in the following table :—

TABLE IV  
*Showing the Effects of Oxygenation and De-oxygenation on Five Different Samples of Blood*

Saline concentration (per cent.)	Percentage Hæmolysis.				
	0·410	0·410	0·395	0·395	0·380
Venous blood . . . . .	32	22	61	47	67
Oxygenated blood . . . . .	10	6	22	7	11
De-oxygenated blood . . . . .	12	6	23	8	10

It is here seen that removal of gases from venous blood has the same effect as oxygenation, viz. an increase in the resistance of the cells. Furthermore, this increase is quantitatively the same for oxygenated and de-oxygenated blood, which makes one strongly suspect that oxygenation (or de-oxygenation) are coincidental rather than fundamental factors. Both have one thing in common; they will tend to remove dissolved gases of which carbon dioxide is the most important. The classical inertness of nitrogen makes it unlikely that this gas plays any important part.

Loss of carbon dioxide from the blood will result in a rise in pH, and, in the experiments described in Table IV, a considerable change of pH actually occurred. The pH of each mixture of blood and saline was determined with the following results :—

- Venous blood . . . . . pH range = 7·50—7·54
- Oxygenated blood . . . . . pH range = 7·93—8·03
- De-oxygenated blood . . . . . pH range = 7·95—8·10

It is therefore reasonable to conclude that the increased fragility in each case is due to a common cause, and that cause is the loss of carbon dioxide and consequent rise in pH.

The converse process, exposure of blood to an atmosphere of carbon dioxide, has already been shown by Dacie and Vaughan, to produce a marked increase in the fragility of the cells.

If this argument is correct, then the use of a buffered hæmolysing system should substantially reduce the effects of changes caused by the removal of carbon dioxide, provided that these changes are reversible—for oxygenation (or removal of carbon dioxide) alters the pH of the original whole blood, whilst the influence of any hæmolysing system does not come into play until after the blood is mixed with it.

Theoretical consideration shows that no one stable inorganic salt exists which is capable of functioning as a buffer against both hydrogen

and hydroxyl ions at  $pH$  ranges of 7.2-7.6. Rather than revert to amphoteric organic compounds (*e.g.* glycine) it was decided to experiment with phosphate buffers. The ideal hæmolysing system would have all its osmotic pressure derived from salts capable of functioning as buffers, so that the greatest possible buffering capacity would be present in a given hypotonic solution. A system meeting these requirements is found in a solution containing the two sodium phosphates,  $NaH_2PO_4$  and  $Na_2HPO_4$ . Since the crystalline form of the monosodium salt is hydrated, the corresponding potassium salt,  $KH_2PO_4$  is used instead.

In the following experiments, the hæmolysing system consisted of a mixture of  $Na_2HPO_4$  and  $KH_2PO_4$  of varying  $pH$ , but of constant molarity ( $M/28.5$ ). In all cases, 0.50 c.c. of blood, venous or oxygenated, was added to 9.50 c.c. of the buffer solution and the mixture was allowed to stand for two hours before the percentage hæmolysis in each tube was determined.

TABLE V

*Showing the Absence of Effect of Oxygenation when Hæmolysis of Erythrocytes is Carried Out at Constant pH*

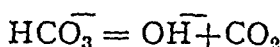
	$pH$ of the Original Buffer.	$pH$ of the Blood-Buffer Mixture.	Percentage Hæmolysis.
Venous blood . . .	7.32	7.30	80
Oxygenated blood . .	7.32	7.33	83
Venous blood . . .	7.51	7.49	56
Oxygenated blood . .	7.51	7.50	58
Venous blood . . .	7.70	7.62	33
Oxygenated blood . .	7.70	7.68	37

At first sight it appears that oxygenation under conditions of constant  $pH$  increases slightly the degree of hæmolysis. It is impossible in such experiments, with the low concentrations of salt necessary to give some degree of hæmolysis, to have a buffer system sufficiently powerful to control the  $pH$  to within 0.01 unit. The  $pH$  of the systems containing oxygenated blood is always a little higher than that of the corresponding systems containing venous blood, due to the loss of carbon dioxide during oxygenation. It will be seen that this difference in  $pH$  is roughly proportional to the differences between the extent of hæmolysis in venous and oxygenated blood. This again suggests that these differences are related to a loss of carbon dioxide and to a change in  $pH$ ; and leaves little doubt that oxygenation *per se* has no effect upon hæmolysis.

When carbon dioxide escapes from the cell into the atmosphere, via the plasma, it is well known that chloride distribution is simultaneously altered by the migration of chloride ion from cell to plasma (the "Chloride Shift" of Hamburger). During oxygenation of blood

in a tonometer, the same chloride shift is found to occur. In one such experiment, the plasma chloride (expressed as NaCl) increased from 611 mgm. per cent. to 665 mgm. per cent. This chloride increase, even if not balanced by other ionic changes, would produce a change in chloride concentration of the blood-saline hæmolysing system of only 0.0016 gm. per cent.—an increase which would have no significance on the percentage hæmolysis. The chloride shift accompanying oxygenation is merely an incidental phenomenon and not a cause of the altered fragility.

The carbon dioxide of venous blood is very largely in the form of bicarbonate ion. This ion breaks up, *in vivo* or *in vitro*, according to the equation:—



The carbon dioxide escapes into the gaseous phase, leaving the hydroxyl ions to produce an increase in *pH*. A pure aqueous solution of sodium bicarbonate loses carbon dioxide into the atmosphere, or into a vacuum, very slowly. Meldrum and Roughton (1932) showed that the liberation of carbon dioxide from bicarbonate in blood is greatly accelerated by the presence in the erythrocytes of the enzyme carbonic anhydrase.

If the changes described above during oxygenation are due to the loss of carbon dioxide, one would expect them to be directly related to the activity of this enzyme. Like all enzymes, carbonic anhydrase is sensitive to certain enzyme poisons, and Keilin and Mann (1941) have shown that it is especially sensitive to potassium cyanide and to sulphanilamide. Experiments using potassium cyanide have been inconclusive. It is a salt which undergoes extensive salt hydrolysis, and its addition causes serious alterations in *pH* in a sodium chloride hæmolysing system. Sulphanilamide has been found to be preferable as an enzyme poison; it appears to have no specific hæmolysing action, nor does it appear to affect the *pH* or the osmotic pressure in the concentrations in which it will inhibit the action of the enzyme.

TABLE VI

*Showing the Effect of Sulphanilamide in Inhibiting the Action of Carbonic Anhydrase, and Preventing the Decrease in Fragility which Occurs after Oxygenation (S = Sulphanilamide).*

Saline concentration (gm. per cent.)	Percentage Hæmolysis.					
	0.410	0.395	0.395	0.380	0.380	0.380
S concentration (mg./c.c.)	2.5	2.5	1.2	1.2	4.5	2.2
Venous blood (no S)	56	75	55	69	97	86
Venous blood+S	50	69	55	67	96	85
Oxygenated blood (no S)	9	21	17	29	52	15
Oxygenated blood+S	32	55	31	44	79	39

These results are by no means clear-cut, but they indicate that sulphanilamide, when added to blood in a concentration sufficiently low to have no effect on the osmotic pressure, does, to some extent, inhibit the decrease in fragility which occurs on oxygenation, although this inhibition is by no means complete. However, one could not hope for other than partial success in such an experiment, since bicarbonate is capable of giving off carbon dioxide without the catalytic effect of any enzyme. It is concluded that the action of sulphanilamide in these experiments is due to the poisoning of carbonic anhydrase.

### SUMMARY

1. A method is described for the accurate determination of the percentage hæmolysis which occurs in hypotonic solution.

2. When erythrocytes undergo hæmolysis in hypotonic solution, they obey the "all-or-none" law. The cells either hæmolyse completely, or not at all.

3. The osmotic fragility of human erythrocytes depends upon (i) the saline concentration of the hæmolysing system, (ii) the temperature, (iii) the length of time which the cells are in contact with the saline, and (iv) the  $pH$ .

4. Oxygenation and changes of carbon dioxide content of the blood have no direct effect upon fragility; but since both affect the  $pH$ , they alter the fragility indirectly.

5. Changes in fragility indirectly due to loss of carbon dioxide, can be partially prevented by the addition of sulphanilamide which acts as an inhibitor of the enzyme carbonic anhydrase.

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# MASS RADIOGRAPHY IN GLASGOW

## REPORT ON FIRST 50,000 EXAMINATIONS \*

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THE Glasgow Mass Radiography Unit began active operations in the summer of 1944, and it will be remembered that the autumn meeting of the Tuberculosis Society was held that year at the Mass Radiography Centre, Ashley Street, Glasgow, when a demonstration of the method was given and a discussion held of the administrative and other problems involved. Thereafter, the Unit functioned steadily and it completed its first 50,000 examinations in March 1946. The present talk is based on the cases of tuberculosis found in this group of 50,000.

The group consisted of 25,525 males and 24,475 females, 51·05 and 48·95 per cent. respectively. Its *age and sex distribution* is seen in Table I, which shows that over 60 per cent. of the examinees were

TABLE I  
*Age and Sex Distribution*

Age-Group.	Males.		Females.		Both Sexes.	
	No.	Per Cent.	No.	Per Cent.	No.	Per Cent.
-14	10,703	41·93	10,670	43·60	21,373	42·75
15-19	4,163	16·31	5,576	22·78	9,739	19·48
20-24	1,416	5·55	2,728	11·15	4,144	8·29
25-29	953	3·73	1,574	6·43	2,527	5·05
30-34	1,313	5·14	1,313	5·36	2,626	5·25
35-39	1,514	5·93	953	3·89	2,467	4·93
40-44	1,646	6·45	749	3·06	2,395	4·79
45-49	1,482	5·81	495	2·02	1,977	3·95
50-54	1,055	4·13	236	0·96	1,291	2·58
55-59	779	3·02	115	0·47	894	1·79
60-64	346	1·36	48	0·20	394	0·79
65-	155	0·61	18	0·07	173	0·35
Total	25,525	100·00	24,475	100·00	50,000	100·00

under 20 years of age and that there was a preponderance of females under the age of 30 and a preponderance of males after that age. The reasons for these variations were the emphasis put by the Unit on the examination of younger people, which it was expected would yield a higher amount of active tuberculosis than if the concentration was on older people, the absence on war service of young adult males, the presence of young women in industry, and the comparative withdrawal of women from industry in the older age-groups.

\* Read at a meeting of the Tuberculosis Society of Scotland held in Glasgow on 24th January 1947.

If known pulmonary tuberculosis, which occurred once in about 700 examinations, and obviously calcified lung and root gland lesions, which were noted once in every 30 examinations, are discounted,

TABLE II  
*Incidence of Active Pulmonary Tuberculosis in Age-Groups*

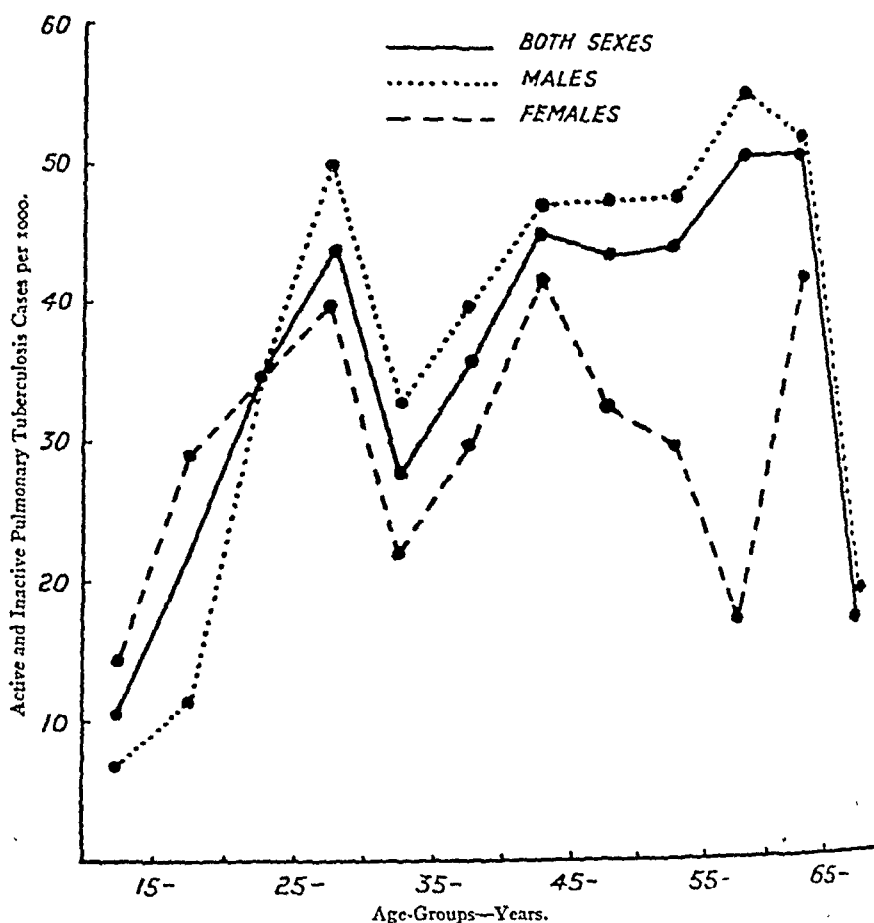
Age-Group.	Males.			Females.			Both Sexes.		
	Total.	Active P.T.		Total.	Active P.T.		Total.	Active P.T.	
		No.	Cases per 1000.		No.	Cases per 1000.		No.	Cases per 1000.
-14	10,703	26	2.4	10,670	64	6.0	21,373	90	4.2
15-19	4,163	26	6.2	5,576	81	14.5	9,739	107	11.0
20-24	1,416	19	13.4	2,728	43	15.8	4,144	62	15.0
25-29	953	9	9.4	1,574	21	13.3	2,527	30	11.9
30-34	1,313	7	5.3	1,313	5	3.8	2,626	12	4.6
35-39	1,514	5	3.3	953	2	2.1	2,467	7	2.8
40-44	1,646	12	7.3	749	5	6.7	2,395	17	7.1
45-49	1,482	6	4.0	495	0	...	1,977	6	3.0
50-54	1,055	9	8.5	236	0	...	1,291	9	7.0
55-59	779	3	3.9	115	0	...	894	3	3.4
60-64	346	1	2.9	48	1	20.9	394	2	5.1
65-	155	0	...	18	0	...	173	0	...
Total	25,525	123	4.8	24,475	222	8.3	50,000	345	6.9

TABLE III  
*Incidence of Inactive Pulmonary Tuberculosis in Age-Groups*

Age-Group.	Males.			Females.			Both Sexes.		
	Total.	Inactive P.T.		Total.	Inactive P.T.		Total.	Inactive P.T.	
		No.	Cases per 1000.		No.	Cases per 1000.		No.	Cases per 1000.
-14	10,703	47	4.4	10,670	91	8.5	21,373	138	6.5
15-19	4,163	22	5.3	5,576	81	14.5	9,739	103	10.6
20-24	1,416	31	21.9	2,728	51	18.7	4,144	82	19.8
25-29	953	38	39.9	1,574	42	26.7	2,527	80	31.7
30-34	1,313	36	27.4	1,313	24	18.3	2,626	60	22.8
35-39	1,514	55	36.3	953	27	27.9	2,467	82	33.2
40-44	1,646	65	39.5	749	26	34.7	2,395	91	38.0
45-49	1,482	64	43.2	495	16	32.3	1,977	80	40.5
50-54	1,055	41	38.9	236	7	29.7	1,291	48	37.2
55-59	779	40	51.4	115	2	17.4	894	42	47.0
60-64	346	17	49.1	48	1	20.9	394	18	45.7
65-	155	3	19.4	18	0	...	173	3	17.3
Total	25,525	459	18.0	24,475	368	15.0	50,000	827	16.5

the incidence of active and inactive pulmonary tuberculosis in the series is found to be as in Table II and Table III respectively. There is a high incidence of active disease, much higher than in the country as a whole, in females in the three age-groups which comprise the

years 15 to 29, in males in the age-group 20 to 24, and to a less extent in the age-group 25 to 29, the incidence in the males being less than in the females. It should be remembered, of course, that many males and not a few females aged 18 to 29 were on National Service and consequently are not represented in the tables which refer only to civilians; a more correct figure would be obtained by consideration of notifications to the Medical Officer of Health which also include patients discovered by mass radiography in the Services. Small secondary rises of active tuberculosis are noted in the age-group



*Incidence of active and inactive pulmonary tuberculosis.*

40 to 44 and again, in males, in the age-group 50 to 54. Inactive tuberculosis is noted more often in females than in males below the age of 20 years, and after that more commonly in males than in females.

These differences may be studied further by reference to the figure, which shows in graphic form the combined incidence of active and inactive disease per 1000 examinees for each age-group and for both sexes.

It is interesting to speculate on the experience of the 30 to 34 age-group, which was born in the years immediately before the 1914-18 war. Does it have a special immunity against pulmonary

tuberculosis, or has it already discarded most of its tuberculous inmates perhaps when the group was much younger than it is now? Again, did its following groups, the 25 to 29 and 20 to 24 age-groups, born during the 1914-18 war and the post-war years, when there was a known high incidence of tuberculosis in the community, acquire an excessive amount of tuberculous infection when its members were young children? In this event, can we expect a low incidence in the future from those born in the 1930's, *i.e.* those represented in the present study as being under 15 years?

Table IV, which shows *the ratio of inactive to active disease* in the various age-groups, suggests that if tuberculosis is noted in the 15 to 19 years age-group there is a half-and-half chance that it is active, and there is also a considerable chance of activity if the person is aged under 30 years, particularly if a woman is concerned.

TABLE IV  
*Ratio of Inactive to Active Tuberculosis*

Age-Group.	Males.	Females.	Both Sexes.
-14 . . .	1.8	1.4	1.5
15-19 . . .	0.8	1.0	1.0
20-24 . . .	1.6	1.2	1.3
25-29 . . .	4.2	2.0	2.7
30-34 . . .	5.1	4.8	5.0
35-39 . . .	11.0	13.5	11.7
40-44 . . .	5.4	5.2	5.4
45-49 . . .	10.7	...	13.3
50-54 . . .	4.6	...	5.3
55-59 . . .	13.3	...	14.0
60-64 . . .	17.0	1.0	9.0
65- . . .	...	...	...
Total . . .	3.7	1.7	2.4

It has been shown (Table II) that there is an increased incidence of active tuberculosis in certain age-groups. Table V, although it suffers from the fact that the numbers of actual cases are too small for valid conclusions to be drawn, and from the absence on National Service of part of the population, is interesting in that it suggests that the peak years are 23 for males and 21 for females. It confirms that there is an increased incidence in both sexes in the later teens and in the greater part of the twenties.

Not all the cases of active pulmonary tuberculosis were admitted to hospital in Glasgow. Many were referred for treatment to the Medical Officer of Health of the area in which they were resident, and others settled down while under observation by the Mass Radiography Unit and the Tuberculosis Dispensary, or while under the care of their own doctors. Of 204 patients, 53 males and 151 females, who received treatment in Glasgow hospitals, and in whom the diagnosis of active pulmonary tuberculosis was confirmed, 44 (21.6 per cent.) gave a history of contact with known tuberculosis, 42 (20.6 per cent.)



had a suspicious previous illness, 118 (57.8 per cent.) had slight localising symptoms, 63 (30.9 per cent.) had slight constitutional symptoms and 94 (46.1 per cent.) showed physical signs suggestive of disease of the lungs.

TABLE V  
*Incidence of Active Pulmonary Tuberculosis in Years under 30*

Age in Years.	Males.			Females			Both Sexes.		
	Total.	Active P.T.		Total.	Active P.T.		Total.	Active P.T.	
		No.	Cases per 1000.		No.	Cases per 1000.		No.	Cases per 1000.
12	297	0	...	337	3	8.9	634	3	4.7
13	7,822	17	2.2	7,930	46	5.8	15,752	63	4.0
14	2,577	9	3.5	2,399	15	6.3	4,976	24	4.8
15	1,395	4	2.9	1,413	11	7.8	2,808	15	5.3
16	1,104	7	6.3	1,258	22	17.5	2,362	29	12.3
17	709	4	5.6	1,003	18	17.9	1,712	22	12.9
18	490	4	8.2	981	14	14.3	1,471	18	12.2
19	465	7	15.1	921	16	17.4	1,386	23	16.6
20	442	2	4.5	741	12	16.2	1,183	14	11.8
21	327	5	15.3	613	14	22.8	940	19	20.2
22	255	4	15.7	468	6	12.8	723	10	13.8
23	196	5	25.5	431	5	11.6	627	10	15.9
24	196	3	15.3	475	6	12.6	671	9	13.4
25	179	3	16.8	339	6	17.7	518	9	17.4
26	165	1	6.1	314	7	22.3	479	8	16.7
27	175	2	11.4	325	3	9.2	500	5	10.0
28	196	1	5.1	306	1	3.3	502	2	4.0
29	238	2	8.4	290	4	13.8	528	6	11.4
Total	17,228	80	4.6	20,544	209	10.2	37,772	289	7.7

TABLE VI  
*Active Pulmonary Tuberculosis—Hospital Patients  
Suggestive Preceding Illness*

	53 Males.	151 Females.	204 Both Sexes.
Pleurisy . . . . .	4	13	17
Basal pain . . . . .	1	8	9
Shoulder pain . . . . .	2	4	6
Spontaneous pneumothorax . . . . .	1	...	1
Erythema nodosum . . . . .	1	4	5
Cervical adenitis . . . . .	...	2	2
Suprasternal abscess . . . . .	...	1	1
Ganglion of wrist . . . . .	...	1	1
Total . . . . .	9	33	42

Table VI shows that pleurisy was the commonest suggestive preceding illness and a history of basal chest pain and of shoulder pain, both also indicative of pleurisy, was elicited in almost an equal number of other patients. Erythema nodosum was noted much less commonly.

*Symptoms* were rarely taken account of by the patients. Localising symptoms (Table VII) when present were slight and often attributed to some such cause as smoking in the cases of cough and hoarseness or huskiness. The commonest localising symptoms were cough (including in that term morning clearing of the throat), scanty sputum,

TABLE VII  
*Active Pulmonary Tuberculosis—Hospital Patients*  
*Localising Symptoms*

	Males.	Females.	Both Sexes.
Total patients . . . . .	53	151	204
Patients with symptoms . . . . .	35	83	118
Cough . . . . .	27	59	86
Sputum . . . . .	16	23	39
Dyspnœa . . . . .	7	23	30
Basal pain . . . . .	8	16	24
Shoulder pain . . . . .	...	16	16
Huskiness . . . . .	6	10	16
Cold . . . . .	5	5	10
Hæmoptysis . . . . .	3	1	4
Epistaxis . . . . .	...	1	1
Laryngitis . . . . .	...	1	1

slight dyspnœa after exercise, basal or shoulder pain and huskiness of voice. A positive sputum was found in ten patients, of whom only one was under the age of 20 years. Symptoms, whether localising or

TABLE VIII  
*Active Pulmonary Tuberculosis—Hospital Patients*  
*Constitutional Symptoms*

	Males.	Females.	Both Sexes.
Total patients . . . . .	53	151	204
Patients with symptoms . . . . .	17	46	63
Lassitude . . . . .	10	27	37
Loss of flesh . . . . .	9	12	21
Anorexia . . . . .	3	11	14
Sweating . . . . .	3	8	11
Pallor . . . . .	3	6	9
Amenorrhœa . . . . .	...	5	5
Menorrhagia . . . . .	...	2	2
Recent mental backwardness . . . . .	0	1	1

constitutional, were found rather more commonly in the older people than in those under 20 years of age.

Constitutional symptoms are shown in Table VIII. The commonest were noted to be lassitude, loss of flesh, anorexia, sweating and pallor. Menstrual disturbance did not bulk largely in the symptomatology, probably for the reason that nearly half of the female patients were

of ages 16 and under, when menstruation in many cases had not become established.

*Physical signs* in the active cases treated in hospital are summarised in Table IX. Of individual signs, those elicited with the stethoscope were the most valuable, especially variations in the respiratory murmur, bronchophony and pectoriloquy. Pyrexia of small degree, usually about 99° F., was noted in a few cases.

Table X shows *the distribution of the lung lesions* according to the extent of the disease. It is seen that, of 146 patients aged 19 years and under, 106 patients had unilateral disease, 72·7 per cent., whereas of 58 patients aged 20 years and over, 34 patients, or only 58·6 per cent., had unilateral disease. Even with the use of mass radiography of the

TABLE IX  
*Active Pulmonary Tuberculosis—Hospital Patients*  
*Physical Signs*

	Males.	Females.	Both Sexes.
Total patients . . . . .	53	151	204
Patients with signs . . . . .	21	73	94
Findings consistent with P.T. . . . .	7	23	30
Findings suggestive of disease . . . . .	14	50	64
Prolonged expiratory part of R.M. . . . .	3	21	24
Tubular R.M. . . . .	4	8	12
Cog-wheel breathing . . . . .	1	3	4
Increased V.R. . . . .	2	0	2
Whispered pectoriloquy . . . . .	2	4	6
Rhonchi . . . . .	1	1	2
Friction . . . . .	0	1	1
Diminished resonance . . . . .	1	3	4
Oedema of vocal cord . . . . .	1	0	1
Huskiness . . . . .	0	1	1
Pyrexia . . . . .	1	11	12
Pallor . . . . .	0	2	2
Debility . . . . .	0	1	1
V.S. pulmonic murmur . . . . .	0	1	1
Mitral stenosis . . . . .	0	1	1

supposedly healthy population it would appear that we are not yet detecting pulmonary tuberculosis as soon as we would wish. Again, too many cases are at the stage of frank cavitation when we see them, and this applies as much to the youngest children as to older persons; the true primary lesion is seldom seen in its acute phase.

While it is true that some of the patients have fairly extensive disease showing considerable breakdown, on the whole the patients discovered by mass radiography methods do not require to spend such a long time in hospital as those discovered as the result of investigation of suspicious symptoms. Accordingly, there is less demand for hospital accommodation by them; for example, the Glasgow Unit, while working at a rate of about 30,000 examinations per year during the period covered by this report, made use of about 50 female beds

and 25 male beds for the treatment of its cases of active tuberculosis. It was also found that it was seldom necessary to send patients to

TABLE X

*Active Pulmonary Tuberculosis—Hospital Patients  
Distribution of Lung Lesions*

	19 Years and Under.			20 Years and Over.			All Ages.		
	Male.	Female.	Both Sexes.	Male.	Female.	Both Sexes.	Male.	Female.	Both Sexes.
R 1 . . . .	2	14	16	3	8	11	5	22	27
R 1, 2 . . . .	1	18	19	4	7	11	5	25	30
R 1, 2, 3 . . . .	...	1	1	...	...	...	...	1	1
R 2 . . . .	5	8	13	...	...	...	5	8	13
R 2, 3 . . . .	1	...	1	...	...	...	1	...	1
R 3 . . . .	1	2	3	...	...	...	1	2	3
R, effusion . . . .	...	1	1	...	...	...	...	1	1
Total, Right . . . .	10	44	54	7	15	22	17	59	76
L 1 . . . .	4	14	18	3	2	5	7	16	23
L 1, 2 . . . .	3	14	17	3	3	6	6	17	23
L 1, 2, 3 . . . .	...	2	2	...	1	1	...	3	3
L 2 . . . .	5	8	13	...	...	...	5	8	13
L 3 . . . .	1	1	2	...	...	...	1	1	2
Total, Left . . . .	13	39	52	6	6	12	19	45	64
R 1, L 1 . . . .	2	4	6	...	3	3	2	7	9
R 1; L 1, 2 . . . .	1	7	8	1	...	1	2	7	9
R 1, 2; L 1 . . . .	1	3	4	2	3	5	3	6	9
R 1, 2; L 1, 2 . . . .	2	10	12	6	5	11	8	15	23
R 1, 2; L 1, 2, 3 . . . .	...	...	...	...	1	1	...	1	1
R 1, 2; L 2 . . . .	...	1	1	1	1	2	1	2	3
R 1, 2; L, pleurisy . . . .	...	1	1	...	...	...	...	1	1
R 1, 2, 3; L 1 . . . .	...	...	...	1	...	1	1	...	1
R 1, 2, 3; L 1, 2 . . . .	...	1	1	...	...	...	...	1	1
R 1, 2, 3; L 1, 2, 3 . . . .	...	3	3	...	...	...	...	3	3
R 2; L 1, 2 . . . .	...	1	1	...	...	...	...	1	1
R 2; L 1, 2, 3 . . . .	...	1	1	...	...	...	...	1	1
R 2; L 2 . . . .	...	2	2	...	...	...	...	2	2
Total, Bilateral . . . .	6	34	40	11	13	24	17	47	64
ALL LESIONS . . . .	29	117	146	24	34	58	53	151	204

R = right; L = left.

- 1 = above level of lower border of 2nd costal cartilage in postero-anterior film;  
 2 = below (1) and above level of lower border of 4th costal cartilage;  
 3 = below level of lower border of 4th costal cartilage.

hospital for observation, whether to make a diagnosis or to assess activity of a tuberculous lesion; observation patients were easily controlled from the Unit and rarely required to stop work during their period of observation if they curtailed their movements when off work.

of ages 16 and under, when menstruation in many cases had not become established.

*Physical signs* in the active cases treated in hospital are summarised in Table IX. Of individual signs, those elicited with the stethoscope were the most valuable, especially variations in the respiratory murmur, bronchophony and pectoriloquy. Pyrexia of small degree, usually about 99° F., was noted in a few cases.

Table X shows *the distribution of the lung lesions* according to the extent of the disease. It is seen that, of 146 patients aged 19 years and under, 106 patients had unilateral disease, 72·7 per cent., whereas of 58 patients aged 20 years and over, 34 patients, or only 58·6 per cent., had unilateral disease. Even with the use of mass radiography of the

TABLE IX  
*Active Pulmonary Tuberculosis—Hospital Patients*  
*Physical Signs*

	Males.	Females.	Both Sexes.
Total patients . . . . .	53	151	204
Patients with signs . . . . .	21	73	94
Findings consistent with P.T. . . . .	7	23	30
Findings suggestive of disease . . . . .	14	50	64
Prolonged expiratory part of R.M. . . . .	3	21	24
Tubular R.M. . . . .	4	8	12
Cog-wheel breathing . . . . .	1	3	4
Increased V.R. . . . .	2	0	2
Whispered pectoriloquy . . . . .	2	4	6
Rhonchi . . . . .	1	1	2
Friction . . . . .	0	1	1
Diminished resonance . . . . .	1	3	4
Œdema of vocal cord . . . . .	1	0	1
Huskiness . . . . .	0	1	1
Pyrexia . . . . .	1	11	12
Pallor . . . . .	0	2	2
Debility . . . . .	0	1	1
V.S. pulmonic murmur . . . . .	0	1	1
Mitral stenosis . . . . .	0	1	1

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TABLE X  
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*Distribution of Lung Lesions*

	19 Years and Under.			20 Years and Over.			All Ages.		
	Male.	Female.	Both Sexes.	Male.	Female.	Both Sexes.	Male.	Female.	Both Sexes.
R 1 . . . . .	2	14	16	3	8	11	5	22	27
R 1, 2 . . . . .	1	18	19	4	7	11	5	25	30
R 1, 2, 3 . . . . .	...	1	1	...	...	...	...	1	1
R 2 . . . . .	5	8	13	...	...	...	5	8	13
R 2, 3 . . . . .	1	...	1	...	...	...	1	...	1
R 3 . . . . .	1	2	3	...	...	...	1	2	3
R, effusion . . . . .	...	1	1	...	...	...	...	1	1
Total, Right . . . . .	10	44	54	7	15	22	17	59	76
L 1 . . . . .	4	14	18	3	2	5	7	16	23
L 1, 2 . . . . .	3	14	17	3	3	6	6	17	23
L 1, 2, 3 . . . . .	...	2	2	...	1	1	...	3	3
L 2 . . . . .	5	8	13	...	...	...	5	8	13
L 3 . . . . .	1	1	2	...	...	...	1	1	2
Total, Left . . . . .	13	39	52	6	6	12	19	45	64
R 1, L 1 . . . . .	2	4	6	...	3	3	2	7	9
R 1; L 1, 2 . . . . .	1	7	8	1	...	1	2	7	9
R 1, 2; L 1 . . . . .	1	3	4	2	3	5	3	6	9
R 1, 2; L 1, 2 . . . . .	2	10	12	6	5	11	8	15	23
R 1, 2; L 1, 2, 3 . . . . .	...	...	...	...	1	1	...	1	1
R 1, 2; L 2 . . . . .	...	1	1	1	1	2	1	2	3
R 1, 2; L, pleurisy . . . . .	...	1	1	...	...	...	...	1	1
R 1, 2, 3; L 1 . . . . .	...	...	...	1	...	1	1	...	1
R 1, 2, 3; L 1, 2 . . . . .	...	1	1	...	...	...	...	1	1
R 1, 2, 3; L 1, 2, 3 . . . . .	...	3	3	...	...	...	...	3	3
R 2; L 1, 2 . . . . .	...	1	1	...	...	...	...	1	1
R 2; L 1, 2, 3 . . . . .	...	1	1	...	...	...	...	1	1
R 2; L 2 . . . . .	...	2	2	...	...	...	...	2	2
Total, Bilateral . . . . .	6	34	40	11	13	24	17	47	64
ALL LESIONS . . . . .	29	117	146	24	34	58	53	151	204

R = right; L = left.

- 1 = above level of lower border of 2nd costal cartilage in postero-anterior film;  
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hospital for observation, whether to make a diagnosis or to assess activity of a tuberculous lesion; observation patients were easily controlled from the Unit and rarely required to stop work during their period of observation if they curtailed their movements when off work.

## TREATMENT OF PLACENTA PRÆVIA \*

A REVIEW OF CASES TREATED IN THE EDINBURGH ROYAL MATERNITY HOSPITAL AND SIMPSON MEMORIAL PAVILION, THE ROYAL INFIRMARY, EDINBURGH, DURING THE YEARS 1926-1945

By JOHN STURROCK, M.B., Ch.B., F.R.C.S.Ed., F.R.C.O.G.

Assistant Obstetrician and Gynæcologist, The Royal Infirmary, Edinburgh

MR PRESIDENT and Fellows, when asked by the Council of the Edinburgh Obstetrical Society to take part in this discussion I was specifically requested to prepare from the Medical and Clinical Reports<sup>1</sup> a short statistical review of the cases of placenta prævia treated in the old Edinburgh Royal Maternity Hospital and the new Simpson Maternity Pavilion of the Edinburgh Royal Infirmary, so I beg you to bear with me while I present figures. I would express my thanks to the President, Dr Haultain and Dr Sheppard who helped me to collect these figures.

I have chosen the twenty years 1926-45 inclusive and divided them into four five-year periods so as to examine the trend of maternal and foetal mortality rates and compare varying preferences in the methods of treatment. The cases came under the care of the member of the staff who happened to be on duty when they were admitted, so the figures represent the work of the staff as a whole.

In 1925 and again in 1937, papers on the treatment of placenta prævia were read before the Edinburgh Obstetrical Society and both had an important influence on the practice in the hospitals.

Professor B. P. Watson and Dr Douglas Miller<sup>2</sup> in 1925 reviewed 254 cases, treated for the most part in the Edinburgh Royal Maternity Hospital, with a maternal mortality of 9.8 per cent. and a foetal mortality of 67 per cent, and I have included their figures in my first table. These authors advocated that the treatment of all such cases should be undertaken in a maternity hospital or fully equipped nursing home and that they should be admitted after the initial hæmorrhage, before serious blood loss had occurred. In considering the results of the different methods of treatment they pointed out that these were best for both mother and baby if rupture of the membranes or cæsarean section would probably be extended. These authors even hinted at series, but it was suggested that if the necessity for admission to hospital was appreciated and acted upon, the indications for cæsarean section would probably be extended. These authors even hinted at the possibility in hospital, of expectant treatment, of cases under 34 weeks' gestation where the initial bleeding had ceased, so that

\* Read at a combined meeting of the Edinburgh Obstetrical Society and the Glasgow Obstetrical and Gynæcological Society, held in Edinburgh, 9th May 1947.

the chances of the baby might be improved. There was no mention of blood transfusion in this paper.

TABLE I.—Table I compares the maternal and foetal mortality in the different five-year periods. It shows the fairly constant number of cases admitted since 1926. It also shows a fall in maternal mortality which is striking and a fall in foetal mortality in the last two five-year periods which is not so dramatic as the improvement in the maternal figures, but significant in cases delivered after the 36th week.

TABLE I

Years.	Numbers.	Maternal Deaths.	Foetal Deaths.		
			Total.	After 36th Week.	
		Per cent.	Per cent.	Per cent.	
1914-24 . .	254	25 9·8	171 67	...	
1926-30 . .	188	14 7·4	120 in 190 63	59 in 121	50
1931-35 . .	209	10 4·7	141 in 211 67	63 in 114	55
1936-40 . .	203	6 3·0	114 in 205 56	52 in 129	40
1941-45 . .	228	2 0·8	93 in 235 39	35 in 129	27

TABLE II.—Booked cases: the rise in the number of booked cases corresponds to the general increase of this category dealt with by the hospital. The maternal death rate is not improved as much as one might have expected, but the total figures are small, and after all, the emergency invariably began in the patients' own homes, just as in the non-booked cases. The foetal death rate in the last group is

TABLE II  
*Booked Cases*

Years.	No. of Cases.	Maternal Deaths.	Foetal Deaths.	
			Per cent.	Per cent.
1927-30 . .	26	0	10 38	
1931-35 . .	44	1 2·2	28 63	
1936-40 . .	51	2 4·0	26 in 52	50
1941-45 . .	65	1 1·5	19 29	

noteworthy as it is 10 per cent. lower than the figure for the total booked and non-booked cases, and almost bears comparison with the Belfast figures to be referred to shortly.

Tables III, IV, V and VI are concerned with the methods of treatment employed and their results in the four five-year periods.

TABLE III (1926-30).—Table III indicates that the vaginal methods of delivery were the commonly accepted lines of treatment, although caesarean section was being practised occasionally, even when the period of gestation was under 36 weeks and the placenta prævia not of the complete type. It shows the high maternal and very heavy



foetal mortality associated with plugging the lower uterine segment with the half breech.

TABLE III

1926-1930

No. of cases . . . . .	188	Per cent.
Maternal Mortality . . . . .	14	7.4
Foetal Mortality . . . . .	120 in 190	63
Foetal Mortality (after 36th week) . . . . .	59 in 121	50

	Methods of Treatment.			Maternal Mortality.	Foetal Mortality.		
	Total.	Before 36th Week.	After 36th Week.		Total.	Before 36th Week.	After 36th Week.
Caesarean section . . . . .	27	5	22	1	9	5	4
Leg down (previously packed 12) . . . . .	110	49	61	7	88	45	43
Willet's forceps . . . . .	3	0	3	1	1	0	1
Pack . . . . .	13	5	8	2	9	4	5
Membs. rupt. or nil . . . . .	34	10	24	3	13	7	6
Bag . . . . .	1	0	1	0	0	0	0

TABLE IV (1931-35).—In Table IV it is seen that more cases were being treated by rupture of the membranes, or if that failed to control hæmorrhage, by the application of Willett's forceps. It was being

TABLE IV

1931-1935

No. of Cases . . . . .	209	Per cent.
Maternity Mortality . . . . .	10	4.7
Foetal Mortality . . . . .	141 in 211	67.4
Foetal Mortality (after 36th week) . . . . .	63 in 114	55

	Methods of Treatment.			Maternal Mortality.	Foetal Mortality		
	Total.	Before 36th Week.	After 36th Week.		Total.	Before 36th Week.	After 36th Week.
Cæsarean section . . . . .	22	5	17	0	7	3	4
Leg down (previously packed 6) . . . . .	83	46	37	9	76	42	34
Willet's forceps (previously packed 3) . . . . .	37	16	21	1	19	9	10
Pack . . . . .	10	5	5	0	7	4	3
Membs. rupt. or nil . . . . .	57	23	34	0	32	20	12

appreciated that the minor degrees of placenta prævia were often over-treated. Cæsarean section was still limited in use to the complete and major degrees of partial placenta prævia, especially if the chances of the child's survival by virtue of its maturity, were reasonable. The maternal and foetal mortality from plugging with the half breech remained high.

By now blood transfusion was being used more often, aided greatly by J. R. Copland's Voluntary Donor List organised in 1929. It took time, however, to get a donor from the relatives or the donor list and draw the blood. Also it was seldom that there was more than one pint available for a case.

The late Professor James Hendry and Professor Dugald Baird,<sup>3</sup> in their paper to the Edinburgh Obstetrical Society in 1937, re-emphasised the great necessity for co-operation between the general practitioners and the hospital staff to ensure early hospitalisation of all cases of ante-partum hæmorrhage and thereafter the highest grade of team work on the part of the hospital staff. They were insistent that there was no place for the domestic treatment of ante-partum hæmorrhage, and that no case should be examined vaginally except in a properly equipped theatre and then only by a person of

TABLE V

1936-1940

No. of Cases . . . . .	203	Per cent.
Maternal Mortality . . . . .	6	3
Fœtal Mortality . . . . .	114 in 205	56
Fœtal Mortality (after 36th week) . . . . .	52 in 129	40

	Methods of Treatment.			Maternal Mortality.	Fœtal Mortality.		
	Total.	Before 36th Week.	After 36th Week.		Total.	Before 36th Week.	After 36th Week.
Cæsarean section . . . . .	53	14	39	1	21	11	10
Leg down (previously packed o) . . . . .	39	22	17	3	37	21	16
Willeit's forceps . . . . .	44	16	28	0	27	14	13
Pack and obstet. forceps . . . . .	1	0	1	1	1	0	1
Membs. rupt. or nil . . . . .	66	22	44	1	28	16	12

experience who could forthwith undertake any active treatment deemed necessary. They advocated, from personal experience supported by excellent figures, wider indications for cæsarean section and showed how essential was an efficient and prompt blood transfusion service. These views were largely adopted in the practice of the old Edinburgh Maternity Hospital and from March 1939 in the new Maternity Pavilion of the Royal Infirmary. The establishment of the Blood Bank at the Royal Infirmary in 1939 was of great importance in ensuring speedier and more adequate transfusion.

TABLE V (1936-40) and TABLE VI (1941-45).—Examination of the two last five-year periods shows a steady improvement in results as these principles of treatment were more clearly appreciated and employed. Yet there were two maternal deaths in the New Pavilion following plugging the lower uterine segment with the half breech, in spite of the close proximity to the Blood Bank being fully exploited.

TABLE VII.—Table VII indicates the causes of maternal deaths in relation to the methods of treatment. Hæmorrhage and shock

TABLE VI

1941-1945

No. of Cases . . . . .	228	Per cent.
Maternal Mortality . . . . .	2	0.8
Fœtal Mortality . . . . .	93 in 235	39.5
Fœtal Mortality (after 36th week) . . . . .	35 in 139	27.0

	Methods of Treatment.			Maternal Mortality.	Fœtal Mortality.		
	Total.	Before 36th Week.	After 36th Week.		Total.	Before 36th Week.	After 36th Week.
Cæsarean section . . . . .	74	28	46	1	13	8	5
Leg down (previously packed o) . . . . .	33	21	12	0	33	20	13
Willet's forceps . . . . .	47	17	30	1	19	12	7
Membs. rupt. or nil . . . . .	74	33	41	0	28	18	10

TABLE VII

*Causes of Maternal Deaths in Relation to Methods of Treatment*

	1926-30.	1931-35.	1936-40.	1941-45.
<i>Total Deaths</i> . . . . .	14	10	6	2
<i>Hæmorrhage and Shock</i> . . . . .	10	9	5	1
Pack. Leg down . . . . .	3	4	...	...
(Transfused) . . . . .	(1)	(3)	...	...
Leg down . . . . .	2	5	3	...
(Transfused) . . . . .	...	(3)	(3)	...
Pack. Forceps . . . . .	1	...	1	...
(Transfused) . . . . .	(1)	...	(1)	...
Pack. Undelivered . . . . .	1	...	...	...
(Transfused) . . . . .	(1)	...	...	...
Willet's forceps . . . . .	1	...	...	...
Membs. rupt. . . . .	2	...	1	...
Cæsarean section . . . . .	...	...	...	1
(Transfused) . . . . .	...	...	...	(1)
<i>Sepsis</i> . . . . .	4	1	0	0
Leg down . . . . .	2	...	...	...
Willet's forceps . . . . .	...	1	...	...
Membs. rupt. . . . .	1	...	...	...
Cæsarean section . . . . .	1	...	...	...
<i>Pulmonary Embolism</i> . . . . .	...	...	...	...
Cæsarean section . . . . .	...	...	1	...
<i>Post-Anæsthetic Vomiting and Shock</i> . . . . .	...	...	...	...
Willet's forceps . . . . .	...	...	...	1

have been gradually reduced by the adoption of the modern management in all its details. Reading the case reports of death from hæmorrhage and shock one is impressed with the similar pattern they present. Most commonly plugging with the half breech was



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the method of treatment employed and although efficient in controlling bleeding at the time, within five hours of delivery the patient had collapsed and died, despite blood transfusion. These cases always strike one as bearing some similarity to the cases of prolonged third stage where, in the absence of much, or indeed sometimes any, bleeding, a state of shock may suddenly develop. In these latter, manual removal of the placenta after a blood transfusion usually reverses the deterioration, but in the cases of placenta prævia the shock develops after completion of the third stage even if bleeding is slight, and the degree of shock seems much more often to be irreversible in spite of transfusion. Post-mortem examination of these cases in this series did not show uterine rupture. An understanding of the mechanism of these fatalities and their remedy would re-establish one's confidence in plugging the lower uterine segment with the half breech in multi-paræ with very premature children and in the teaching of this method to those who must practise where no maternity hospitals are available, for it has its merits.

Sepsis as a cause of death has been reduced and follows the fall in the morbidity rate of the hospital.

1926-30 morbidity rate 6.9 per cent.

1931-35     "     "     7.7     "

1936-40     "     "     4.5     "

1941-45     "     "     3.6     "

The sulphanilamides have undoubtedly played an important part here, as well as the considerable limitation of the vaginal methods of treatment to rupture of the membranes and Willett's forceps.

Fœtal scalp traction has gained popularity in the hospital as it can often be employed as an efficient alternative to bringing down a leg for the control of hæmorrhage and at a lower cost in fœtal life. There has been no indication to view the method with disfavour on account of sepsis, especially due to a *Bacillus Welchii* infection (F. J. Browne<sup>4</sup>).

In the 1941-45 group there were two maternal deaths. The first was a primigravida aged 31 who was treated for bleeding in hospital for ten days at the 26th week of gestation and was re-admitted at the 31st week with slight bleeding which stopped. She remained in hospital till the 35th week when labour began with spontaneous rupture of the membranes. Eight hours later a classical cæsarean section was done under nitrous oxide, oxygen and ether anæsthesia because of a recurrence of bleeding and a failure of the head to descend. The placenta partially covered the internal os. Severe post-partum hæmorrhage occurred as the patient was being lifted from the operating table on to the trolley and was followed by collapse which failed to respond to blood transfusion.

The second case was a primigravida æt. 23 who was admitted at the 37th week of pregnancy with bleeding due to a placenta prævia which partially covered the internal os. The membranes were ruptured

and Willett's forceps were applied under gas and oxygen anæsthesia and the bleeding controlled. Much vomiting and tachycardia followed this interference and continued despite intravenous glucose and gastric lavage. Spontaneous delivery of a still-born child occurred fifty-four hours later with immediate collapse and death of the mother. Post-mortem examination showed only evidence of acute terminal heart failure.

With the increasing employment of abdominal delivery it is useful to remember that the long-term influence of cæsarean section done for placenta prævia on subsequent pregnancies and labours was referred to by Hendry and Baird in their paper and compared very favourably with the results following vaginal treatment and delivery. It is of interest to find that 40 cases of uterine rupture were dealt with by the hospital during the years 1926 to 1945, and in 11 of these a previous cæsarean section scar had given way. Of these 11 the indication for cæsarean section was placenta prævia in 3. Two of these patients died so there is what might be termed a delayed mortality rate attendant on the wider use of abdominal delivery. Practically all the cæsarean sections done for the cases of placenta prævia under review were classical.

TABLE VIII.—Table VIII compares the maternal and foetal death rates in five hospitals. The arresting figure is the low foetal death rate reported by Macafee of Belfast.<sup>5</sup> Two factors were significant in the production of his excellent results.

TABLE VIII  
*Comparison of Maternal and Fœtal Mortality*

Hospitals.	No. of Cases.	Maternal Deaths.	Fœtal Deaths.
		Per cent.	Per cent.
Belfast R.M.H., 1937-44, Macafee . . .	174	1 0·5	41 23·5
Rotunda, Dublin, 1941-45 . . .	153	3 2·0	54 35·3
Glasgow M.H., 1941-45 . . .	413	16 3·8	156 37·7
Edinburgh S.M.M.P., 1941-45 . . .	228	2 0·8	93 39·0
Manchester, St Mary's, 1941-45 . . .	269	9 3·3	94 34·4

In the first place Macafee was given the supervision of all cases of ante-partum hæmorrhage and personally directed a team which individualised the treatment of each case within the limits of Macafee's accumulating personal experience. Secondly, placenta prævia ceased to be considered an obstetrical emergency which must necessarily be dealt with at the first hæmorrhage. In other words, the conservative management of cases of ante-partum hæmorrhage, with delay in making digital exploration of the lower segment essential to differentiate accidental from unavoidable hæmorrhage, was employed in over 50 per cent. of cases. This prolongation of gestation saved the lives of many babies.

In Edinburgh the conservative attitude to the management of cases of ante-partum hæmorrhage has gained a little ground in recent years, although for a long time Jaggard's dictum, "There is no expectant plan of treatment for placenta prævia," was almost the rule.

During the 1941-45 period 41 or 6·2 per cent. of the 674 cases of ante-partum hæmorrhage were treated conservatively by delaying digital examination where bleeding had ceased after admission. Fourteen of the 41 cases of ante-partum hæmorrhage were eventually diagnosed as due to placenta prævia, *i.e.* only 6·1 per cent. of the total 228 cases of placenta prævia were treated conservatively as compared with over 50 per cent. in the Belfast series. The reduction in our foetal mortality rate from over 65 per cent. as it used to be is partly due to the greater use of cæsarean section in the major degrees and avoiding over-treatment of the minor cases, but the improved management of the premature child under the direction of the pædiatricians also plays a part. In the light of Macafee's experience, however, the scope of conservatism has to be considered, but, apart from the possibility of ultimate disappointment because of the greater incidence of congenital foetal deformities associated with placenta prævia, it means a heavy demand on an already grossly overworked antenatal in-patient department, which can only be remedied by increasing still further the number of antenatal beds so urgently awaited to accommodate the many other complications of pregnancy best dealt with in hospital. Nor is conservatism even in hospital without a definite risk to the mother. One of the two maternal deaths in the last five-year's period occurred in such a case although it is doubtful if the conservatism *per se* could be blamed, yet a massive and even fatal hæmorrhage can occur.

One feels that Macafee has been fortunate when he could write: "Among these patients there has been nothing to confirm the belief that recurrent hæmorrhages tend to lead up to a catastrophic hæmorrhage. Many patients have been under observation for weeks during which numerous small hæmorrhages have occurred without causing any serious anxiety."

There can be no doubt that adoption of this plan of conservatism is bound to put heavy additional strain on resident medical and nursing staff of a maternity hospital, possibly housing several such cases at one time, because of the close vigilance required and the smooth and speedy application of appropriate treatment essential in the presence of the sudden further hæmorrhage which must occur if the placenta lies prævia.

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## A REVIEW OF CASES TREATED IN THE GLASGOW ROYAL MATERNITY HOSPITAL, 1941-1946

### A. THE MATERNAL ASPECT

By HUGH STIRLING, M.B., Ch.B., M.R.C.O.G. (Glasgow)

I HAVE the honour and pleasure to introduce the following figures from the records of the Glasgow Royal Maternity and Women's Hospital.

These figures represent a survey, conducted by Dr Tennent and myself, of all cases of placenta prævia admitted to the hospital in the six-year period 1941 to 1946.

Dr Tennent will shortly give you his figures and comments on foetal mortality and other points of related interest; I will confine my remarks to the maternal aspect of placenta prævia.

We have divided our cases into two groups—mild and severe, as we consider this distinction essential before attempting any assessment of results.

*Mild cases* are those in which the placenta did not reach to the edge of (or overlap in any way) the internal os, when the latter was one to two fingers dilated.

*The severe group* includes all cases in which the placenta was either over the os, or its margin lay within one inch of it.

The mild group therefore corresponds to "lateral placenta prævia," and the severe group includes the "marginal," "complete" and "central" types.

We have not used these common terms, because there does exist some difference of opinion as to their exact meaning, and because, from the practical point of view, the distinctions are often of academic interest only.

Further, as in the vast majority of the cases in our series the condition was ante-partum and the patient not in labour, the os was usually only one finger dilated (or multiparous os) and rarely was it more dilated than two fingers.

The severe cases, therefore, are those in which, in these conditions, placental tissue was easily felt by the examining finger, without anæsthetising the patient.

It is advocated by some that to confirm, indeed to make, the diagnosis of placenta prævia, examination under anæsthesia is essential, the whole hand being inserted into the vagina and the lower segment thoroughly explored.

This was not so in our series, anæsthetic examination being necessary in only 1 to 2 per cent. of the cases in the severe group.

We do not, therefore, believe that examination under anæsthesia should be carried out as a routine measure, as, while minor degrees of low implantation may not be confirmed by ordinary digital examination per vaginam, most of the severe degrees can be thus detected,

and the impalpable minor degrees are of relatively little practical importance.

Uroselectan and Perabrodil were not employed in any of the cases in the series.

This consecutive series consists of 505 cases of placenta prævia, of which 222 were classed as mild and 283 as severe.

With regard to *Incidence*, no reliable figures can be given, as the hospital incidence is out of all proportion to that occurring generally. Comyns Berkeley's estimate of 1 : 1000 cases is probably still fairly accurate, and though the hospital numbers have gone up, this is the result of policy rather than a rise in incidence generally.

*Parity*.—Of our 505 cases, 84 occurred in primigravidæ and 421 in multiparæ. In the former group, 53 were mild and 31 severe cases. In the latter, 169 were of mild and 252 of severe degree.

Apart, therefore, from the much higher incidence of the condition in multiparæ, the severe types also occurred much more often than in primigravidæ.

In *Age Grouping* we found that, in primigravidæ, there were 13 cases in the decade 21 to 30 years, and 31 cases between 31 to 40 years, these two decades together accounting for 88 per cent. of all cases. However, the proportion of severe cases was much increased in the latter age group, *i.e.* 31 to 40 years.

In multiparæ, in the group 21 to 30 years there were 135 cases; in group 31 to 40 years 237 cases; and over 40 years, 49 cases. Again, with increasing age, there was a marked increase of the severe degrees of placenta prævia.

Increasing age, therefore, would seem to be of some importance, though obviously there is a close association between multiparity and the higher ages.

*Maturity* of the pregnancy at the time of the first bleeding was investigated and average figures worked out. These figures corresponded closely in primigravidæ and multiparæ, being 36 weeks' maturity in mild cases, and 34 weeks in severe cases; but considerable range occurred in exceptional cases in each group.

*Third Stage Complications* are recognised to be of frequent occurrence in placenta prævia. In this series there were 24 cases of post-partum hæmorrhage in the mild group, an incidence of 10·8 per cent.; and only 8 cases in the severe group, an incidence of 2·8 per cent. This latter figure is explained by the fact that most of the severe cases were treated by cæsarean section, with consequent control of the uterus and immediate completion of the third stage.

With regard to the blood loss, the cases of P.P.H. were classified as follows: 14 cases of moderate degree; 18 cases of severe degree; in all, 32 cases of P.P.H. (6 per cent. incidence). In 8 cases manual removal of placenta was necessary. There were three deaths.

These figures include 4 cases of secondary P.P.H., 3 of which were in the severe group.

*Blood Transfusion*, as distinct from other restorative measures, was employed in 109 cases, *i.e.* in 21 per cent. of the total series, or in almost 30 per cent. of the severe group alone. One patient died of an incompatible transfusion.

Of these 109 cases, in the mild group 12 were given blood ante-partum and 9 post-partum; and in the severe group, 81 were transfused ante-partum and 7 post-partum.

From the foregoing details it can be deduced that the cases in our series constituted a "mixed bag," with a large incidence of the severer types of placenta prævia. I make this observation before going on to consider, in detail, maternal mortality and morbidity.

**MORTALITY AND MORBIDITY.**—Firstly, taking the series as a whole, there were 18 deaths, a mortality rate of 3·6 per cent. In the mild group (222 cases) there were 4 deaths, 1·8 per cent. mortality. In the severe group (283 cases) there were 14 deaths, 5 per cent. mortality.

With regard to the *causes of death*, combining the two groups:

*Hæmorrhage and shock* accounted for 8 cases, of which 3 were due to P.P.H.; 3 died of *puerperal sepsis*; 2 died of *respiratory infection*; and 3 died *under anæsthesia*, on the operating table. In addition one case died (undelivered) of *acute cardiac failure*, and one case died (undelivered) following an *incompatible transfusion*.

In all, 4 cases died "unavoidably," *i.e.* 2 within half an hour of admission to hospital (one case died within ten minutes and one was B.B.O. with retained placenta); one case of cardiac disease, *not* blood-loss; and one of acute pulmonary œdema, *not* directly due to placenta prævia.

Deducting these cases, the *corrected mortality rates* therefore are:

Total series . . . . .	2·8 per cent.
Mild group . . . . .	0·9 "
Severe group . . . . .	4·2 "

By way of comparison, F. J. Browne quotes the results of eleven teaching hospitals as follows: Total cases, 3103; overall mortality, 5·9 per cent.; partial P.P., 4·4 per cent.; complete P.P., 11·8 per cent. Stratz, employing the method of bipolar version, claimed a mortality of 0·6 per cent. in 173 cases; and Macafee, in 174 cases, a mortality of only 0·57 per cent.

Secondly, with regard to *morbidity*, complications in the puerperium occurred in 69 cases *in toto*, giving an overall rate of 13·7 per cent. In the mild group there were 20 cases, an incidence of 9 per cent.; and in the severe group 49 cases, a morbidity of 17·3 per cent.

These figures include all types of post-natal complication and are therefore somewhat high. Excluding all "non-notifiable"

conditions the *morbidity rates* are: Total series, 10 per cent.; mild group, 5.4 per cent.; severe group, 13.8 per cent.

With regard to the *causes of morbidity* we found that: 17 cases were due to respiratory infection; 8 to puerperal sepsis; 6 to wound sepsis; 3 to localised utero-vaginal sepsis; 6 to urinary infection; 5 to thrombophlebitis; 2 to secondary P.P.H.; 2 to mastitis; and 18 were described as P.U.O. The last were probably of mild infectious origin, but all investigations were negative.

**METHODS OF TREATMENT.**—The results obtained with different methods of treatment were classified, and the following figures abstracted:—

#### *Mild Group*

No treatment . . .	120 cases; 2 deaths (1.66 per cent.); 5 morbid
A.R.M. . . . .	65 " 2 " (3.0 " ); 6 "
Packing . . . .	3 " ... " 1 "
Version . . . .	7 " ... " ...
Cæsarean section .	27 " ... " 5 "

The deaths occurred in the two largest groups and, of these 4 fatal cases, 2 were "unavoidable." The *corrected mortality*, therefore, is 0.8 per cent. in the "no treatment" group and 1.5 per cent. in the "A.R.M." group, the others being nil.

The choice of treatment in these mild cases does not, therefore, appear to be of first importance.

For comparison, the results obtained in the previously quoted series (F. J. Browne) were: A.R.M., 2.1 per cent. mortality; Willett's forceps, 3.5 per cent.; version, 0.9 per cent.; hydrostatic bag, 5 per cent. The Willett's forceps method has never been popular in Glasgow and was not employed in any case in our series. The hydrostatic bag is regarded as a museum piece.

#### *Severe Group*

No treatment . . .	4 cases; 2 deaths (50.0 per cent.); 0 morbid
Packing . . . .	2 " ; ...
Version . . . .	25 " ; 3 " (12.0 " ); 4 "
Cæsarean section .	252 " ; 9 " (3.6 " ); 45 "

One death was "unavoidable" in the "no treatment" group, dying ten minutes after admission. One death in the "cæsarean section" group was due to the anæsthetic, giving a corrected mortality of 3.2 per cent. Cæsarean section, therefore, seems to be easily the best procedure in the severe cases, giving the lowest maternal mortality.

This now brings me to a consideration of the *delayed or expectant treatment* of placenta prævia. Delay is of course undertaken in the interests of the child. Dr Tennent will go into this point fully and will indicate our attitude and our joint conclusions. My present object is merely to try to assess the added risks, if any, to the mother when delay is adopted. It is to be understood that where delayed treatment was undertaken, the patient was retained under close

observation, facilities for transfusion were at hand, and treatment could be instituted immediately.

First, we had to determine what we would class as "delayed treatment." After considering this point from several angles, we decided that we would define treatment as "delayed" in those cases where it was not carried out within twenty-four hours of admission to hospital.

It may be objected that, in so doing, we have included in our delayed group some cases in which the delay was not intentional, and many more where it was unsuccessful.

We considered, however, that as placenta prævia is generally reckoned to be a serious obstetrical emergency, some form of active treatment would be instituted within twenty-four hours of admission unless delay was thought justifiable. Within twenty-four hours every case, even though collapsed on admission, ought to be in a fit enough state for active treatment.

Secondly, we considered that where delay in a case was adopted, and perhaps two or three days later, recurrent or continued hæmorrhage made active treatment imperative, then such a case was a failure of the delayed method and should be included as such in the delayed treatment group.

With this explanation of our definition in mind, the figures obtained for "immediate" and "delayed" treatment are as follows :—

#### *Mortality*

##### *Mild Group*

Immediate—151 cases ; 3 death —2.0 per cent. ; *corrected* 0.66 per cent.

Delayed — 71 cases ; 1 death —1.4 " ; " 1.4 "

##### *Severe Group*

Immediate—216 cases ; 9 deaths—4.1 per cent. ; *corrected* 3.7 per cent.

Delayed — 67 cases ; 5 deaths—7.5 " ; " 4.5 "

The *corrected* rates shown were obtained by deducting the "unavoidable" deaths, which do not affect the issue here between the two forms of treatment.

There is, therefore, a slight *increase* in the maternal mortality in the delayed treatment, this being largely accounted for by failures in that group.

#### *Morbidity*

##### *Mild Group.*

Immediate—151 cases ; 12 morbid—8.0 per cent. ; "notifiable"—6 per cent.

Delayed—71 cases ; 8 morbid—11.4 per cent. ; "notifiable"—4.2 per cent.

##### *Severe Group.*

Immediate—216 cases ; 32 morbid—14.8 per cent. ; "notifiable"—12.7 per cent.

Delayed—67 cases ; 17 morbid—25.4 per cent. ; "notifiable"—18.0 per cent.

In the mild cases, therefore, the morbidity rates were about the same in the two groups. In the severe cases, morbidity rate was considerably higher in the delayed group than in the immediate.

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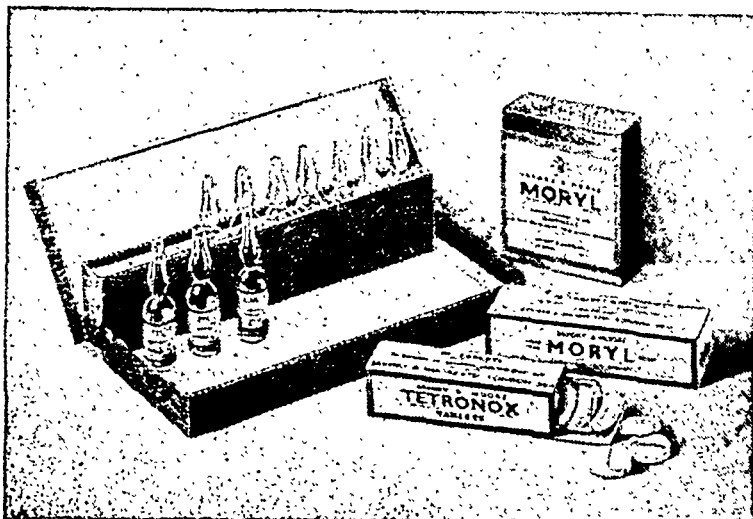
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Puerperal sepsis—of the septicæmic type—was, it is interesting to note, confined to the immediate group.

With regard to the methods of treatment employed, there was no indication that any one method was more suited to immediate than to delayed treatment, or vice versa.

In general terms, therefore, these figures appear to show that some slight but definite added risk to the mother ensues when delay in treatment is adopted.

Finally, it may be of interest to note the results from *cæsarean section* in particular, and from the use, in these cases, of general and spinal anæsthesia.

In the *mild group* of cases, 27 sections were performed with no mortality. In several of these cases, however, placenta prævia was not the condition of primary importance.

In the *severe group*, 252 sections were performed with 9 deaths in all, a mortality of 3·6 per cent. The overall mortality, in 279 cases, was 3·2 per cent.

The lower segment operation was performed in 9 cases, with one death.

ANÆSTHESIA.—In the *severe group alone*, spinal analgesia was employed in 82 cases, general anæsthesia in 170. There was one death on the operating table in the spinal series, giving a mortality of 1·25 per cent. There was one death under general anæsthesia, a mortality of 0·6 per cent.

There was one death on the table, in which a spinal had been given but to which chloroform was added because of complaint of pain when the abdomen was being closed. This patient was a primigravida, aged 41 years, and she had a pre-eclamptic toxæmia. Post-mortem, the only notable lesion was "pre-eclamptic mottling of the liver."

I have not included this case in the comparison of anæsthetics, there being a doubt as to which caused death, though personally I would attribute the latter to the chloroform.

Taking into account the deaths occurring after operation, there was only one additional death, from sepsis, in the spinal series. In the general series there were 5 more deaths, 2 from pneumonia, 2 from secondary hæmorrhage, and one from sepsis and ileus.

Fatal complications were therefore more common after general than after spinal anæsthesia.

While it is true that general anæsthesia may have been used in some cases where spinal was considered undesirable, the results from the use of the latter do *not* indicate (contrary to general belief) that spinal analgesia is highly dangerous in the type of case under review.

In concluding, though I have given you some comment and occasionally indicated an opinion, I feel that you must hear Dr Tennent's evidence before any summing up is possible.

I therefore leave our conclusions to be presented by him in due course.



## B. THE FŒTAL ASPECT

By ROBERT A. TENNENT, M.B., Ch.B., M.R.C.O.G. (Glasgow)

THERE were 507 infants born in the cases of placenta prævia which Dr Stirling has been discussing. Of these 334 or 65·9 per cent. left the hospital alive, 77 or 15·2 per cent. were stillborn, and 96 or 18·9 per cent. died during the neonatal period. Thus the combined stillbirth and neonatal death rate was 34·1 per cent.

Among the cases suffering from what we have termed a mild degree of placenta prævia, 220 infants were born—74·5 per cent. of these survived, 13·5 per cent. were stillborn and 12 per cent. died in the neonatal period. The corresponding figures for the 287 infants born in the severe group were 59·2 per cent. survivals, 16·4 per cent. stillborn and 24·4 per cent. neonatal deaths. The outlook, therefore, was much more favourable for the infants in the mild group—a foetal mortality of 25·5 per cent. against 40·8 per cent. in the severe group. This is, I think, as one would expect.

INCIDENCE OF TWINS.—Twin pregnancy was noted eight times in the series—an incidence of 1 in 63·1, which is probably higher than normal.

FŒTAL ABNORMALITIES.—The following foetal abnormalities were noted :—

Anencephaly . . . .	3 times
Hydrocephalus . . . .	once
Talipes . . . . .	once
Hydrops foetalis . . . .	once
Exomphalos . . . . .	once
Mongolism . . . . .	once

I have made no correction in the stillbirth or neonatal death rate on this account, as I believe these cases form part of an inevitable foetal mortality which must be expected in any similar group of cases.

BIRTH WEIGHT AND FŒTAL MORTALITY.—An endeavour was made to find out how the infants fared according to their birth weights. The results were as follows :—

	Total No.	S.B. Per Cent.	N.N.D. Per Cent.	Foetal Mortality Per Cent.
Under 2 lb. . . . .	2	100·0	...	100·0
2 lb. and over, but under 3 lb. . . . .	12	6·7	83·3	100·0
3 " " " 4 " " " . . . . .	38	21·0	60·5	81·5
4 " " " 5 " " " . . . . .	73	26·0	41·1	67·1
5 " " " 6 " " " . . . . .	111	18·9	22·5	41·4
6 " " " 7 " " " . . . . .	116	8·6	3·4	12·0
7 " " " 8 " " " . . . . .	97	9·2	2·1	11·3
8 lb. and over . . . . .	58	10·3	3·5	13·8

From this the following points are noteworthy :—

1. The foetal mortality remains very considerable until 6 lb. when there is a sharp decline from 41·4 to 12 per cent., in which region it remains.
2. This sharp decline is more marked in the neonatal death rate—from 22·5 to 3·4 per cent.
3. The stillbirth rate shows a more gradual fall and reaches an approximate level of 9 per cent. at which level it remains in the last three weight groups.
4. The stillbirth rate forms the greater portion of the foetal mortality in infants over 6 lb.

These figures support the already well-known fact that prematurity is the major danger to the infant in placenta prævia. If the foetus can attain a weight of 6 lb. it will have overcome, to a large extent, the danger of neonatal death, but will still have to face the considerable risk, 9 to 10 per cent., of being stillborn.

METHODS OF IMPROVING FŒTAL MORTALITY.—It seems to me that there are three ways in which the foetal mortality might be improved :—

- (a) Trying to ensure that the infants will attain a birth weight of 6 lb.
- (b) Trying to ensure the survival of the maximum number of infants born weighing under 6 lb. This will largely fall to the pædiatrician, but something might conceivably be done in the matter of maternal nutrition, which might influence what Bourne has called the "birth vigour" of these infants.
- (c) Trying to decrease the stillbirth rate.

The success of any method, from the foetal point of view, should therefore, in my opinion, be judged on :—

1. The number of infants over 6 lb.
2. The number of infants under 6 lb. surviving.
3. The stillbirth rate.

RESULTS OF METHODS OF TREATMENT.—In our hospital the main methods of treating placenta prævia have been, in the mild cases, no treatment and puncture of membranes, and, in the severe cases, cæsarean section. Other methods have been used, but not in sufficient numbers to warrant comparison. However, a reasonable number have had treatment delayed for a varying period over twenty-four hours up to eight weeks. We hold that this can only have been done in the interests of the foetus and that in these cases it was, in the first instance, determined to follow an expectant line of treatment, though later occurrences, such as further bleeding, may have made the obstetrician decide to change this course. We have referred to this, as you have heard, as the delayed treatment.

I have attempted first of all to set down the results of the various methods of treatment, according to whether the cases were mild or severe. Secondly, I have considered the cases of severe degree treated by cæsarean section, in considerable detail, and have contrasted the results of immediate and delayed treatment. Thirdly, I have contrasted the result of immediate and delayed treatment in the entire series.

A. Cases in which no treatment was instituted.

*Mild degree.* 120 infants. 21 S.B. (17·5 per cent.); 15 N.N.D. (12·5 per cent.). Foetal mortality 30 per cent.

Number of infants weighing under 6 lb.—51 (42·5 per cent.).

Number of infants weighing under 6 lb. born alive—33.

Neonatal death rate under 6 lb.—39·4 per cent.

*Severe degree.* 2 cases—1 S.B.; 1 alive and survived.

I should like to draw attention to the high stillbirth rate and low neonatal death rate in these cases.

B. Cases in which puncture of the membranes was performed before or during labour. *All cases were of mild degree.*

There were 63 infants. 5 S.B. (8 per cent.); 10 N.N.D. (16 per cent.). Foetal mortality 24 per cent.

Number of infants under 6 lb.—20 (31·7 per cent.).

Number of infants under 6 lb. born alive—17.

Neonatal death rate under 6 lb.—41·2 per cent.

The lowest foetal mortality was obtained in these cases.

C. The next group to be considered are those in which the treatment was version and bringing down a leg.

*Mild degree.* 7 infants. 2 S.B. (28·6 per cent.); N.N.D., 0.

Number of infants under 6 lb.—3.

*Severe degree.* 23 infants. 20 S.B. (84·3 per cent.); 3 N.N.D. (15·7 per cent.). Foetal mortality 100 per cent.

19 infants weighed under 6 lb.

Thus version would appear reasonable treatment in cases of mild degree—from the foetal point of view—with a foetal mortality of 28·6 per cent., but in the severe group, where the mortality was 100 per cent., it appears to offer little hope of foetal survival. It must be remembered, however, when one considers the small number of cases so treated, that probably the operators adopted this course to avoid cæsarean section, as foetal survival seemed to them unlikely.

D. Five infants presented by the breech in cases of severe degree and a leg was brought down to control the bleeding. All were stillborn. Four weighed under 6 lb. The same remarks apply to these as have been made in the cases of version.

E. Packing was the method adopted in 3 cases.

All infants survived. One weighed under 6 lb.

F. *Cæsarean section.* I now come to the cases treated by cæsarean section, which, as you have heard, was the method chosen for delivery in by far the largest majority of the severe cases. The practice of the obstetricians, with few exceptions, has obviously been to perform cæsarean section in all cases of placenta prævia where the placenta could be felt near the internal os. From the fœtal point of view the results have been reasonably satisfactory.

*Cases of Mild Degree.*—I shall consider the cases of mild degree separately, as I consider they constitute a separate problem, as the placenta prævia has not been the main indication for operation. Indeed some of them gave no history of ante-partum hæmorrhage and the placenta prævia was accidentally discovered during operation for contracted pelvis.

There were 27 infants. 2 S.B. (7·4 per cent.); 1 N.N.D. (3·7 per cent.). Fœtal mortality 11·1 per cent.

Nine infants weighed under 6 lb.

Seven of these were born alive.

One died in the neonatal period.

Neonatal death rate under 6 lb. (14·3 per cent.).

*Cases of Severe Degree.*—In the cases of severe degree there were 257 infants.

22 S.B. (8·5 per cent.) and 66 (25·7 per cent.) died in the neonatal period. The total fœtal mortality was 34·2 per cent.

197 of these infants were delivered within twenty-four hours of admission to hospital.

16 of these were S.B. (8·1 per cent.).

47 were N.N.D. (23·9 per cent.).

Fœtal mortality—32 per cent.

94 of these infants weighed under 6 lb. (47·7 per cent.).

86 were born alive, but 44 or 51·2 per cent. died in the neonatal period.

In 60 infants delivery was postponed for periods over twenty-four hours and sometimes up to seven weeks.

6 of these were S.B. (10 per cent.).

19 of these were N.N.D. (31·7 per cent.).

Fœtal mortality—41·7 per cent.

33 infants weighed under 6 lb.—55 per cent.

31 of these were born alive, but 19 or 61·3 per cent. died during the neonatal period.

27 or 45 per cent. of the infants reached a birth weight of over 6 lb.

4 or 14·8 per cent. were S.B., but there were no neonatal deaths.

The most noteworthy fact in these figures is that, in the cases of severe degree treated by cæsarean section within twenty-four hours, 68 per cent. of the infants left the hospital alive, which, considering the various hazards, is satisfactory.

The results in the cases where cæsarean section was delayed over twenty-four hours and upwards are much less satisfactory.

**CRITICISM OF EXPECTANT METHOD.**—When expectant treatment is adopted, a case may terminate in various ways and may be of either mild or severe degree. To get a correct picture of the results, all cases in the series were divided in two groups—immediate and delayed—according to whether treatment had been instituted or delivery had occurred within twenty-four hours of admission, or whether the delayed treatment had been followed.

They are as follows :—

	Infants.	Survived Per Cent.	S.B. Per Cent.	N.N.D. Per Cent.	Fœtal Mortality Per Cent.
Immediate . . .	368	68·8	15·2	16·0	31·2
Delayed . . .	139	58·3	15·1	26·6	41·7

Infants weighing under 6 lb. :—

Immediate . . .	160 (43·5 per cent.)
Delayed . . .	76 (54·7 per cent.)

N.N.D. rate under 6 lb. :—

Immediate . . .	43·9 per cent.
Delayed . . .	55·7 per cent.

The results are generally worse in the delayed group. It would, therefore, appear that to institute delayed treatment on behalf of the child is a speculative procedure. Of 139 infants in this group, 76 failed to reach the relatively safe weight of 6 lb. I tried to calculate from the entire series the chances of the child being over 6 lb. at the various stages of maturity. Over 40 weeks all the infants weighed over 6 lb.; between 38 and 40 weeks 85·8 per cent., but between 36 and 38 weeks only 48·9 per cent. It should be remembered that even if the pregnancy is carried on to the optimum period of over 280 days, in spite of maternal risks, the child still runs, roughly, a 10 per cent. chance of being stillborn.

On the credit side of the expectant treatment, it must be appreciated that 63 infants did reach a birth weight of 6 lb. or over, and in 62 cases pregnancy was continued for at least another seven days (we consider anything less of negligible value to the fœtus). In several cases the period was six to eight weeks. This, no doubt, did improve the fœtal chance of survival, though it might be argued that life *in utero* with

a placenta prævia which is bleeding, or has bled from time to time, is not comparable with that in normal pregnancy.

CONCLUSIONS.—Dr Stirling and I, from the examination of this series from both the maternal and foetal aspects, have come to the conclusion that, as in our series foetal survival appears no more certain in the delayed than in the immediate group, and as the maternal mortality and morbidity are slightly increased in the delayed group, delay in the treatment of placenta prævia is not a justifiable procedure in the majority of cases.

We admit that our results are worse than those Macafee published in the *British Journal of Obstetrics* in August 1945, which gave a maternal mortality of 0.57 per cent. and a foetal mortality of 23.5 per cent. Our series represents the work of all the obstetricians on the staff over six years. How resolutely the expectant treatment is carried out will depend on the fortitude with which the obstetrician views recurrent hæmorrhage. On the whole, in our series, the obstetricians tended to interfere when there was a recurrence of the bleeding, in contradistinction to Macafee, who states that latterly numerous small recurrent hæmorrhages in a patient under observation caused no serious anxiety. We do feel, however, on the basis of this series, that delay in the treatment of placenta prævia does increase the maternal risk. Macafee states that there is a "theoretical" possibility of sudden severe hæmorrhage in a multipara apart from vaginal examination. One of our fatal cases had treatment delayed for over twenty-four hours as hæmorrhage was not severe. She died thirty-six hours after admission from severe vaginal hæmorrhage, in spite of massive and continued blood transfusion. She never became fit enough to consider operation. No vaginal examination was made until after death, when a placenta prævia of severe degree was found. The majority of our cases are multiparæ whose fecundity is proven—it is all too probable that they will have several future pregnancies. The multiparæ in Glasgow are by no means robust—they nearly all suffer from varying degrees of anæmia and malnutrition. They have responsibilities to their previous children and a fatality or prolonged illness in one of them is a social disaster. We feel that if they can be treated as soon as placenta prævia is diagnosed and if the condition is diagnosed as soon as possible after the first hæmorrhage, they will be spared the risks of repeated and perhaps severe hæmorrhage, which they are poorly equipped to withstand in addition to the strain of the actual delivery, which may be cæsarean section.

We feel strongly, while admitting the place of expectant treatment in placenta prævia, that it should be reserved for elderly primigravidæ and women with no living children.

## DISCUSSION

*Dr A. S. Duncan* (Aberdeen) said that when he had heard that this important subject was coming up for discussion, Professor Baird asked him to look into the figures of the Aberdeen Hospital, with special regard to expectant treatment which had been practised in Aberdeen with much greater freedom since the publication of Macafee's paper in 1945. Up to that time it had been more usual to institute treatment as soon as possible after the patient's admission, but from the beginning of 1946 the policy had been changed, and it had been the aim to treat cases of antepartum hæmorrhage expectantly except when circumstances forced an alternative management.

Dr Duncan submitted tables indicating the results as follows :—

ABERDEEN MATERNITY HOSPITAL  
*Fatal Mortality in Placenta Prævia*

		Under 4½ lb.	S.B. or N.N.D.	Mortality Per Cent.
1938-40—Full time	37		15	43
Premature	32	(26)	31	97
1941—Full time	16		3	19
Premature	18	(12)	12	67
1942—Full time	9		1	11
Premature	16	(8)	10	63
1943—Full time	11		3	27
Premature	13	(7)	8	62
1944—Full time	14		0	0
Premature	10	(6)	8	80
1945—Full time	13		0	0
Premature	12	(9)	8	67
1946—Full time	26		4	15
Premature	13	(5)	3	23

*Placenta Prævia 1946 to show the Incidence of Expectant Treatment*

No symptom of bleeding	4
Admitted at 38th week or after	13
Continued bleeding on admission and therefore required immediate treatment	2
In labour on admission or membranes already ruptured	4
Multiparæ at 37 weeks and treated at once	3
Expectant treatment	13
Total cases	39

Dr Duncan pointed out the drop in foetal mortality in the premature group in 1946, and the sudden alteration in that year of the ratio between premature and full-time babies. He claimed that this swing in the ratio was attributable to expectant treatment. He pointed out that of 13 cases treated expectantly, an average continuance of the pregnancy for three weeks per case was found, and as 8 out of the 13 had their initial hæmorrhages between the 33rd and 36th weeks, it was claimed that a three weeks' continuance of the pregnancy was of significant importance. The numbers were too small for conclusions to be drawn but were such as to encourage a continuation of the policy.

*Professor Fairlie* submitted a record of the results of treatment of placenta prævia in the Maternity Department, Royal Infirmary, Dundee, as follows :—

## MATERNITY DEPARTMENT, ROYAL INFIRMARY, DUNDEE

*Placenta Prævia*

Years.	Numbers.	Maternal Deaths.	Fœtal Deaths.
		Per Cent.	Per Cent.
1941-45 . . .	67	2 2·8	29 46·2 Corrected 38·8
1946 . . .	24	0	6 25·0

*Maternal Deaths. (1941-45)—*

Pulmonary embolism . . .	1
Hæmorrhage and shock . . .	1

*Fœtal Deaths. (1941-45)—*

Premature (under 5½ lb.) . . .	23
Anencephalic . . .	2
Abortion (6 months) . . .	1
Atalectasis (mature) . . .	2
Bronchopneumonia (mature) . . .	1

*Fœtal Deaths. (1946)—*

Premature (under 5½ lb.) . . .	4
Gastro-enteritis (mature) . . .	1
Bronchopneumonia (mature) . . .	1

Professor Fairlie thought that expectant treatment was not without maternal risk, and detailed an illustrative case-history when a patient had bled very nearly to death within a very few minutes, whilst at rest in bed, a vaginal examination not having been made.

*Dr de Soldenhoff* detailed statistics in respect of cases treated at Seafeld Hospital, Ayr, and at the Ayrshire Central Hospital, Irvine, as follows :—

Total number of births from 1939 to May 1947 . . . . . 6313

*Placenta Prævia (1939-47)—*

Total number . . . . .	152	2·4 per cent.
Partial placenta prævia . . . . .	97	64·0 "
Central placenta prævia . . . . .	55	36·0 "
Nulliparous . . . . .	25	16·5 "
Parous . . . . .	127	83·5 "
*Maternal mortality . . . . .	4	2·6 "
Fœtal mortality . . . . .	50	33·0 "

*Treatment—*

Cæsarean section . . . . .	56	37·0 per cent.
Of these 49 were classical cæsarean sections which of the total is . . . . .		88·0 "
7 were lower segment cæsarean sections which is of the total . . . . .		12·0 "
Artificial rupture of membranes . . . . .	32	21·0 "
Bi-polar and internal version . . . . .	19	12·5 "
Willet's forceps . . . . .	3	2·0 "
Spontaneous deliveries . . . . .	41	27·0 "
Placenta born before fœtus . . . . .	1	15·0 "

\* Of the four maternal deaths there were three central and one partial placenta prævia. Of the three central placenta prævia, two were treated by classical cæsarean section, and one by lower uterine segment cæsarean section.

The partial placenta prævia was treated by Willett's forceps.



Dr de Soldenhoff thought expectant treatment was good. Of the deaths none were due to expectant treatment, all having been operated on within twenty-four hours. He was fond of the lower segment operation for placenta prævia and he had not found that it was more dangerous. Of the three deaths after cæsarean section two of them were classical and one a lower segment, and that one had had very severe pre-eclampsia, with a huge subcapsular hæmorrhage of the liver. With spinal analgesia he himself never felt safe. He liked local analgesia, with a minimum of sodium pentothal just before the peritoneum was incised. It was tedious and time-consuming, but he had never had any anxiety owing to the anæsthetic.

*Dr Fahmy* (Edinburgh) stated that discussion of such statistical papers required time for careful study. He asked Dr Stirling to clarify his statement in regard to the instance of sepsis following expectant treatment. Dr Fahmy thought the incidence of aggressive sepsis in cases that had been treated expectantly was small, in spite of the theoretical possibility of latent sepsis being present in the blood clot lying in the lower segment.

He was sorry to hear that our Glasgow colleagues condemned expectant treatment so forcibly as he was satisfied that there were cases in which such treatment was justified. Even when hæmorrhage was slight, the highly parous patient should always be classed as a dangerous multipara, and Dr Duncan had referred to this point. With primigravidæ and in low parity women expectant treatment was, in Dr Fahmy's view, justified in many instances provided the patient was kept under close observation. Patients generally wanted the baby, and that view-point should be kept in mind in addition to the purely obstetrical problem of the position of the placenta.

*Dr George Milne* (Carlisle) said that with regard to vaginal examination in a case of placenta prævia, he disagreed with Dr Stirling who did not make the examination under anæsthesia. He thought that the examination in the theatre should be made under anæsthesia as a sharp bleeding might follow in a case of placenta prævia and the delay involved in anæsthetising the patient before operative procedure could be undertaken might have unfortunate consequences for both mother and baby.

He made a plea for the extended use of the lower segment operation in placenta prævia. It allowed of adequate inspection of the lower uterine segment and insured complete removal of the placenta. In addition the stitching of the line of incision afforded an increased measure of control over large bleeding sinuses in the lower uterine segment.

With regard to treatment of less severe cases of placenta prævia by rupture of the membranes, the danger arose in the third stage of labour when incomplete detachment of the placenta or retention of a placental fragment might occur, and it had been his practice to do a manual removal of the placenta if any undue loss occurred in the third stage of labour.

Dr Milne considered the use of spinal anæsthesia in placenta prævia unjustifiable as the fall of blood pressure might become critical if hæmorrhage occurred between the administration of the anæsthetic and the completing of the operation. He preferred to use gas, oxygen and cyclopropane.

*Professor Baird* (Aberdeen) said he had a special interest in this meeting because of the active part he had taken in the meeting ten years ago. In comparing results from different centres, it was important to recognise that

the type of hospital patient differed in different areas. When Glasgow was compared with Edinburgh it would probably be found that, in the former city, the patients were more often seriously debilitated from chronic malnutrition, anæmia, bronchitis, and extreme multiparity, as a result of which deaths from atonic post-partum hæmorrhage were common, even with a normally situated placenta. He thought it obvious that the wise use of cæsarean section and blood transfusion had lowered the maternal mortality in placenta prævia. He did not think that the question of the upper and lower segment operation was of prime importance. The further reduction of maternal mortality in Glasgow would depend to some extent on improvement in the health and physique of the women.

With regard to fœtal mortality, were we going to be content with a figure of over 30 per cent. ? The saving of fœtal life in the last fifteen years had been due largely to a lowering of the stillbirth rate in mature infants as a result of cæsarean section. The hope of further reduction depended on the prevention of prematurity. He had found that the neonatal mortality in premature infants was twice as high in cases of placenta prævia as in prematurity due to all other causes. The small Aberdeen series presented suggested that expectant treatment could be adopted in some cases in the interests of the fœtus without increasing the risk to the mother. At the same time any general advocacy of conservative treatment might be dangerous. He thought that possibly it would be safer in the case of the elderly multipara with a severe degree of placenta prævia to terminate the pregnancy as soon as the general condition of the patient allowed it.

Professor Baird thought that there might be a danger of being influenced too much by statistics. Usually those who had low mortality figures were most inclined to publish them, and this might give rise to rather erroneous impressions, especially if numbers were small.

*Dr Joan Rose* (Edinburgh) said that with regard to conservative treatment all the speakers had indicated that they made use of this method. For her own part she had kept a patient in the antenatal ward for as long as ten weeks, but had never cared to discharge a patient who had had a hæmorrhage due to placenta prævia until she was delivered. *Dr Duncan* had suggested that such a patient might sometimes be allowed to go home, and she would like to ask if it was not considered preferable to keep the patient in hospital under close observation.

To this *Dr Duncan* replied, at the request of the President, that in Aberdeen a few selected patients had been sent home and these patients were all primigravid or para-i; the cervix was inspected by speculum, and, in all but one of them digital vaginal examination had been carried out and had shown the cervix to be closed. Only patients going into the town, not those into the country, were discharged. Whether or not this was safe he would not like to say.

*Mr Telfer Govan* said he had been working on the question of thrombosis and was interested in the action of ions. He had found that thrombosis could be induced in a bleeding vessel within a few seconds by applying  $\frac{1}{2}$  per cent. zinc sulphate and subjecting it to the action of electrolysis produced by a weak current such as could be obtained from an ordinary 12-volt car battery.

This action could even be attained when applied to the surface of a crushed organ such as the liver.

*Professor Farquhar Murray* (Newcastle) felt that a delay of twenty-four hours hardly justified the term "expectant treatment." He considered that a minimum of a week or even a fortnight might so qualify. Many cases of antepartum hæmorrhage believed to be of the accidental type were really due to mild degrees of placenta prævia. He favoured a section in a nulliparous patient, even in mild cases, if the baby was to be saved. He preferred the upper segment operation.

*Professor Lennie* (Glasgow) said that on behalf of the Glasgow Society he wanted to express thanks for this meeting. He hoped that they would have the pleasure of having the Edinburgh Society in Glasgow before long.

Regarding this discussion, he personally was opposed to block treatment: he thought each case should be considered on its merits. Too often one found cæsarean section done for very premature babies which could not possibly survive. The term "central placenta prævia" was one used for justifying a cæsarean section. He had seen a true central placenta prævia only on very rare occasions. Where the child was fully mature it was justified, but it was not justified when the baby could not possibly survive. In a young primigravida he thought it was definitely wrong.

Contrary to other speakers, he thought there was a very definite place for packing. He thought packing was essential when a woman was exsanguinated, bleeding freely and required a blood transfusion—she would die from shock if any other active treatment were adopted.

*The President* said that it appeared that the discussion had fallen into three sections: first, expectant treatment versus cæsarean section; second, lower segment versus classical cæsarean section; and third, spinal versus local or general anæsthesia. Firstly, regarding the lower uterine segment operation, he had always been rather frightened of trying it and, like Professor Farquhar Murray and Professor Lennie, had contented himself with using the upper segment operation. His reasons for this were first that he thought there must be more bleeding, especially if the placenta were on the anterior wall of the lower uterine segment, and therefore the vascularity might be very difficult to deal with. Second, if the placenta was on the anterior wall, then surely by removing the placenta, which one had to do to get through to the baby, the risk to the child's life would be much greater than if one had not to detach the placenta in removing the child. This risk would be all the greater if there was any difficulty in delivery of the head, which sometimes occurred.

The President said he was interested in the Glasgow nomenclature of placenta prævia of severe and mild. He thought this was an easy classification and one which might be adopted. Every textbook and every centre seemed to have a different nomenclature for the degrees of placenta prævia, with the result that examiners and examinees were often discussing absolutely different entities and also statistics from various centres could not be compared easily as the nomenclature differed. Now, to make confusion worse confounded, Professor F. J. Browne had brought out an entirely new type of nomenclature. He thought if the five professors who were now present at the meeting could get together and produce a common nomenclature, this would be accepted for Scotland at any rate and might be accepted for the whole country; he

would suggest the simpler the differentiation of degrees of placenta prævia the better.

With regard to the question of packing, once again he agreed with Professor Lennie that there were quite a number of cases that did require to be packed, especially those who had a long distance to travel. In Edinburgh the statistics showed that there had been only two deaths in cases who had been packed, whereas it was interesting to note from the Glasgow statistics that there had been no morbidity in the cases who had been packed. From this it would seem that the supposed dangers of packing had been overstated principally by obstetricians who had had little experience with this treatment. The President then asked the openers to reply.

*Dr Tennent* replied first. With regard to Dr Fahmy's point of the treatment of the elderly primigravidæ, he had meant that he did not think such treatment should be applied wholesale to the patients as in Glasgow. He said he was interested in Professor Baird's remark that the babies under  $5\frac{1}{2}$  lb. did not do so well in placenta prævia as in other conditions, and he thought this was a point against expectant treatment. Professor Farquhar Murray had asked why they took the period of twenty-four hours as a standard: this was because if a woman was left for two or three days and then operated on in a hurry, this was a woman whose treatment had been delayed intentionally.

*Dr Stirling* said that a good deal of discussion had been provoked. He pointed out that they were not condemning delayed treatment completely but they thought it had a very limited place, and some time they were going to lose a patient because of it. The point was, as Professor Baird had said, that while delayed treatment might be good, yet it was not without its risk. As far as they were concerned, they asked whether the results justified it.

With regard to lower segment operation he had never employed it for the same reasons as Dr Haultain's, but he thought that it was really purely a matter of personal preference. If one was in the habit of performing lower segment operations, then one would get better results because one was accustomed to this technique.

With regard to spinal analgesia, he was merely pointing out that the risks in using it were not as great as people imagined. Regarding sepsis, he meant that the septicæmic type only occurred in the immediately treated group of cases. With regard to examination under anæsthesia, he still did not think it was necessary, and he could not remember ever having done it. If one got separation of the placenta, then the chances of the child developing were reduced. Regarding the question of packing, he was not so sure that this did not cause a great deal of shock. He thought there was a bigger chance of producing shock in a patient by packing her than by leaving her alone. It was undoubtedly necessary in some cases, but he did not consider it a method of choice but only as a last resort.

*Dr Sturrock* said he would only add that they were very conservative in Edinburgh, and it had been the Glasgow obstetricians who had told them what to do to improve figures and so the idea had been to ask the Glasgow Society back to tell Edinburgh what further to do.

He thought the main lessons of the discussion were that they must consider each case on its merits; (b) that there was still a case for avoiding over-treatment; and (c) that conservative treatment gave a good deal of extra anxiety, but that this was no argument for abandoning it.

## NOTES

At the annual meeting of the College, held on 29th October 1947, the following Office-Bearers were elected for the ensuing year:—*President*, Mr Frank E. Jardine; *Vice-President*, Mr James M. Graham, LL.D.; *Secretary and Treasurer*, Mr K. Paterson Brown; *President's Council*, Sir John Fraser, BART., Dr G. Ewart Martin, Mr W. Quarry Wood, Mr Walter Mercer, Professor J. R. Learmonth, C.B.E., Dr W. F. Theodore Haultain, O.B.E. *Representative on the General Medical Council*, Sir Henry Wade, C.M.G., D.S.O. *Conservator of Museum*, Mr James Norman Jackson Hartley, O.B.E. *Convener of Museum Committee*, Mr W. Quarry Wood. *Librarian*, Dr Douglas Guthrie.

At a meeting of the Royal College of Surgeons of Edinburgh, held on 29th October 1947, Mr James M. Graham, President, in the Chair, the following, who passed the requisite examinations, were admitted Fellows: John Aitken, M.B., CH.B. UNIV. GLASG. 1935; Harry Milne Bennett, M.B., B.CH., B.A.O. QUEEN'S UNIV. BELFAST 1940; Samuel Matta Bector, M.B., CH.B. UNIV. CAIRO 1942; Yeshwant Ganpatrao Bodhe, M.B., B.S. UNIV. BOMB. 1942; Essington Shenstone Brawn, M.R.C.S. ENG., L.R.C.P. LOND. 1939; James Edward Scott Carmichael, M.B., CH.B. UNIV. EDIN. 1935, M.R.C.O.G. 1946; Florence Cavanagh, M.B., B.S. UNIV. MELB. 1933; Douglas Henderson Clark, M.B., CH.B. UNIV. GLASG. 1940; John Carter Comline, M.B., CH.B. UNIV. EDIN. 1939; Wilfred Thomas Cumming, M.B., CH.B. UNIV. EDIN. 1935; James Brown Cuthbert, M.B., B.S. UNIV. LOND. 1937; Norman Murray Black Dean, M.B., CH.B. UNIV. EDIN. 1939; Derrick Dencer, M.R.C.S. ENG., L.R.C.P. LOND. 1944; Manibhai Dahyabhai Desai, M.B., B.S. UNIV. MADRAS 1937; George de Lacy Fenwick, M.B., CH.B. UNIV. NEW ZEAL. 1940; William John Fraser, M.B., CH.B. UNIV. EDIN. 1942; Debabrata Ghose, M.B. UNIV. CALC. 1941; Ian Langdale Gregory, M.B., CH.B. UNIV. MANCH. 1943; Alexander Percy Guttman, M.D. UNIV. MANITOBA 1924; James Arthur Victor Hamilton, M.B., CH.B. UNIV. GLASG. 1941; Hussni El Sayed Higazi, M.B., CH.B. UNIV. CAIRO 1939; Richard Malcolm Hugo, M.R.C.S. ENG., L.R.C.P. LOND. 1937, B.M., B.CH. UNIV. OXFORD 1940; John Huston, M.B., B.CH., B.A.O. QUEEN'S UNIV. BELFAST 1923; George Cyril Whitehead James, M.R.C.S. ENG., L.R.C.P. LOND. 1936; James Maxwell Jones, M.B., B.S. UNIV. LOND. 1938; Victor Alexander Faris Martin, M.B., B.CH., B.A.O. QUEEN'S UNIV. BELFAST 1936; Esmond Millington, M.R.C.S. ENG., L.R.C.P. LOND. 1939; John Charles Gibson Moore, M.B., B.CH., B.A.O. TRINITY COLL. DUBLIN 1939; George Murdoch, M.B., CH.B. UNIV. ST ANDREWS 1943; Alexander Muir Murray, M.B., CH.B. UNIV. GLASG. 1935; Michael Patrick McCormack, M.B., CH.B. UNIV. EDIN. 1939; Charles George Gordon Mackay, M.B., CH.B. UNIV. EDIN. 1938; Francis Douglas Mackenzie, M.D., C.M. UNIV. MCGILL Canada 1940; Dwijendra Lal Poddar, M.B. UNIV. CALC. 1942, M.R.C.O.G., LOND. 1946; Ernest Woodward Price, M.B., B.CH. UNIV. CANTAB. 1933; Agnes Rogers Russell, M.B., CH.B. UNIV. GLASG. 1943; William Henry Scrase, M.B., CH.B. UNIV. BIRM. 1945; Emanuel Seidenman, L.R.C.P. AND S. EDIN. (TRIPLE) 1940; Nirod Chandra Sen, M.B. UNIV. CALC. 1943; Naginlal Chhaganlal Shah, M.B., B.S. UNIV. BOMB. 1936; Homa Vahid-Ol-Molk Shaibany, M.R.C.S. ENG., L.R.C.P. LOND. 1939, M.B., B.S. LOND. 1943; Kantilal

Jaggiwan Sheth, M.B., B.S. UNIV. BOMB. 1938; Douglas William Short, M.B., CH.B. UNIV. GLASG. 1941; Frank MacNeill Smith, M.D. UNIV. ALBERTA 1935; Conrad Evan Elwin Stevens, M.B., B.CH., B.A.O. QUEEN'S UNIV. BELFAST 1930; Franklyn Victor Stonham, M.B., B.S. UNIV. MELB. 1929; John Wallace Milne Sutherland, M.B., CH.B. UNIV. ABERDEEN 1934; Alexander Frederick Torrie, M.B., CH.B. UNIV. EDIN. 1942; Sydney Lance Townsend, M.B., B.S. UNIV. MELB. 1936; Hector Maconochie Urquhart, M.B., CH.B. UNIV. EDIN. 1940; Claud Hibbert Vipond, M.D., QUEEN'S UNIV. ONTARIO 1943; Robert Grenier MacLagan Wedderburn, M.B., CH.B. UNIV. EDIN. 1938; Victor Henry Wheble, B.M., B.CH. UNIV. OXFORD 1944; James Stuart Young, M.D., C.M. QUEEN'S UNIV. ONTARIO 1938.

A QUARTERLY meeting of the College was held on Tuesday, 4th November, the President, Dr D. M. Lyon, in the Chair.

Royal College of Physicians of Edinburgh  
Dr Hugh Michael Denne Shepherd (Shanklin, I.o.W.), Dr Philip Maxwell Wood (Halifax, Yorks), Dr John Craig (Aberdeen), Dr John McGhie Rogan (Glasgow), Dr James Macmaster Macfie (Edinburgh), Dr Alistair William Wright (Edinburgh), Dr Charles Cameron (Edinburgh), Dr Neil Macmichael (Edinburgh) and Dr James Alan Longmore Gilbert (Edinburgh) were introduced and took their seats as Fellows of the College.

Drs Jacob David Malan Claassens (Cape Town, S.A.), John Mitchell Watt (Johannesburg, S.A.), Ian Nicoll Sutherland (Edinburgh), Gurbuxsh Singh (Amritsar, India), Richard Oliver Gillhespy (Paisley), John George Macleod (Edinburgh), Graham Malcolm Wilson (Edinburgh), Robert Stevenson Aitken (Aberdeen) and Thomas Gow Brown (Hamilton, Lanarkshire) were elected Fellows of the College.

Drs William Harold Rose (Ontario, Canada), Karl Gerald Wilson James (Jamaica, B.W.I.), Alexander Smith Rankin Stewart (Shotts, Lanarkshire), Jack Rudolph (Pretoria, S.A.), John Alexander Ross (Rainhill, Lancs.), James Bell Hill MacArthur (Nottingham), Ian Hunter Lockhart Gillies (Dumfries), Hector John Taylor Ross (Kidderminster, Worcs), William John Gibson Barrie (Edinburgh), Walter Gray MacDougall (Edinburgh), James Wright Rae (Larbert, Stirlingshire), Keshavarao Krishnarao Datey (New York), Elliot Maurice Heller (Ontario, Canada), Harry Geoffrey Howell Richards (Cullercoats, Northumberland), John Kelman Drummond (Durban, S.A.), Henry George Hobart Houghton (Edinburgh), Niels Pedersen (Edinburgh), Peter Esmond Brown (Bath), John Watson Buchanan (Barnston, Midlothian), Mervyn Wilfrid Archdall (Lampeter, Card., Wales), Thomas Black (Newcastle-upon-Tyne), Godfrey Beckwith Tait (Edinburgh), Arthur William Outram Taylor (Edinburgh), David Edward Williams (Edinburgh), Aneurin Hughes (Swansea), William Lindsay Sharp (London), Alexander Skene (Edinburgh), Hugh Robert Lauder Fraser (Edinburgh), Norman Wemyss Horne (Edinburgh), James Brian Lowe (Edinburgh), Herbert Duncan Ross (Edinburgh), Erich Kahn (London), Malcolm Watt (Wellington, N.Z.), Albert Edward Claireaux (Edinburgh), James William Thomas Pretsell (Surbiton, Surrey), Arthur Gordon Harper (S. Canterbury, N.Z.), Thomas McSkimming Wilson (Edinburgh), Asoke Kumar Das (Calcutta, India), Hugh Cyril William Stringer (Christchurch, N.Z.), John Taylor Randolph Russell (Edinburgh), Constance Catherine Forsyth (Edinburgh) were elected Members of the College.

The Freeland Barbour Fellowship for original investigations carried out in the Laboratory of the College was awarded to Lieut.-Col. W. F. Harvey, C.I.E.

The Wood Bursary for students commencing the study of Medicine at the Edinburgh Medical School was awarded to Thomas Meredith Chalmers.

The Trustees of the Dr Jessie Macgregor Prize in Medical Science announce the award of the prize, value £75, for the present triennial period to Sheila Sherlock, M.D. EDIN., M.R.C.P. LOND., British Post-Graduate Medical School, London, for her work on liver, purpura, and malnutrition in the Ruhr.

## NEW BOOKS

*Intracranial Complications of Ear, Nose and Throat Infections.* By HANS BREMNER, M.D. Pp. xii+444, with 95 illustrations. Chicago: The Year Book Publishers Inc. 1946.

The view currently held that intracranial pyogenic diseases have become unimportant since the advent of chemotherapy and antibiotics is unsound, and any who doubt this statement will find ample evidence to refute their view in the pages of this excellent monograph. In fact it is common experience that, although modern treatment has altered incidence, it has at the same time introduced new problems in diagnosis; the masked case or the delayed reaction come to mind. Here there is a treatise from a man of wide experience, a pupil of Professor Gustav Alexander, which gives much food for thought, with its evidence that all in his line is not yet simple and understandable.

Not the least useful part of the work is the carefully chosen bibliography, which so readily enables the reader to seek authoritative reference to any part of the subject in which he may be especially interested. A general introduction occupies 68 pages, and the rest of the book is taken up with clinical aspects of different diseases, both sections being illustrated with diagrams, X-rays and photographs of a high order, obviously chosen with thought and skill; but the reader who uses the work as a reference will find the excellent index especially valuable.

*Introduction to the Electron Microscope.* By F. E. J. OCKENDEN, M.I.E.E., F.INST.P. Pp. 24, with 27 illustrations. London: Williams & Norgate Ltd. 1946. Price 2s. 6d. net.

The electron microscope, still in its infancy, offers enormous potentialities for advancement of knowledge. Present types give great resolution and extreme flexibility and can magnify 100 times more than an optical system. Theoretically still greater magnification should be possible. This new instrument of research deserves the attention of all scientists.

The writer describes in simple language the principles on which the apparatus works and then gives an account of the machine itself and tells of some of the discoveries made with its aid. The pamphlet is well illustrated and some excellent photographs show the possibilities of the new apparatus.

*Practical Points in Penicillin Treatment.* By G. E. BEAUMONT, D.M., F.R.C.P., and K. N. V. PALMER, M.B., M.R.C.P. Pp. iii+16. London: J. & A. Churchill Ltd. 1946. Price 1s. 6d.

This small brochure describes the various preparations of penicillin available, also their dosage and method of administration. Then follows a short account of the special features of the treatment of certain disorders. It should be of great assistance to those whose experience of this new remedy has been limited.

*Penicillin in General Practice.* By J. L. HAMILTON-PATERSON, M.D. Pp. 95, with 10 figures. London: Staples Press Ltd. 1946. Price 5s.

The author points out that penicillin is a unique type of therapeutic agent and the rules governing its use are different from those of any other drug. For this reason it is necessary to have a sound knowledge of its properties and the principles which govern its administration. These are set forth in detail in the earlier chapters. The remainder of the book describes the use of penicillin in various specific disorders. The author has brought together the latest information on the subject and has made it readily accessible to the reader.

*Spanish-English Medical Dictionary.* By MAURICE McELLIGOTT, F.R.C.S. (IRELAND), D.P.H. Pp. viii+250. London: H. K. Lewis & Co. 1946. Price 12s. 6d.

This handy-sized dictionary contains some 14,000 Spanish medical terms with their English equivalents. There is also a short list of terms employed in veterinary work. The book is well produced and seems very comprehensive. It is proposed to follow with a similar volume translating English into Spanish.

*Diabetes.* By H. J. JOHN, M.A., M.D., F.A.C.P. Pp. 300, with 73 figures. London: Henry Kimpton. 1946. Price 17s. net.

Though diabetes is an infrequent problem in everyday practice and may not be well understood, a little knowledge of the basic principles of treatment will allow the practitioner to work in the necessary details with safety and a fair degree of precision. These basic principles the author has tried to develop and emphasise. He gives an excellent account of the problems involved and discusses the various special types of case that may occur. Some sixty pages are devoted to dieting, the details of which are clearly presented.

The book is a review of personal experience and as such is very valuable.

*Peptic Ulcer: Diagnosis and Treatment.* By I. W. HELD, M.D., F.A.C.P., and A. A. GOLDBLOOM, M.D., F.A.C.P. Pp. ix+382, with 110 figures. Springfield: Chas. C. Thomas. 1946. Price \$6.50.

This monograph deals with peptic ulcer in all its manifestations. The first six chapters discuss pathogenesis, symptomatology and diagnosis. Many etiological factors are mentioned and the authors state that peptic ulcer does not develop without some underlying constitutional or psychosomatic element. Differential diagnosis receives special attention. In treatment the writers follow standard lines, giving emphasis to a modified form of the Sippy diet. Special types of simple and complicated ulcer are described in detail. The subject is well handled and there is a full list of references for further study.

This work can be thoroughly recommended to specialist and practitioner alike.

*Doctors Differ.* By HARLEY WILLIAMS. Pp. 253. London: Jonathan Cape. 1946. Price 12s. 6d.

Dr Harley Williams, now well known as a successful author, has produced five studies in contrast with John Elliotson, Hugh Owen Thomas, James Mackenzie, William Macewen and R. W. Philip as principal characters. He presents his heroes as agonists, fighting a battle to strengthen the whole human hold on life. With personalities like these, he says, excessive veneration can be avoided and worldly distinctions, degrees and honours minimised in face of their true achievement. His theme is that the way to progress in medicine lies through different temperaments. With his different characters so different in type he contrasts others, Wakley, Mesmer, Braid, Robert Jones, Osler, Horsley and Trudeau.

The work, though written for the general public, will appeal to medical readers and especially to those interested in Scottish Medicine.



## NEW EDITIONS

*Text Book of Physiology.* By W. D. ZOETHOUT and W. W. TUTTLE. Ninth Edition. Pp. 723, with 304 text illustrations and 6 colour plates. London: Henry Kimpton. 1946. Price 25s.

This is a "middle-weight" textbook designed for students of Medicine, Dental Surgery and Pharmacy who do not seek honours in the subject. The authors are two American professors with long experience of teaching. The book is a concise, yet accurate, statement of the elements of physiology, and the students, for whom it is designed, will find within it a sufficiency of factual knowledge to equip them for their professional work. The figures and illustrations are numerous and good and the general turn-out of the book very satisfactory, considering the comparatively cheap price.

*Diseases of the Nervous System.* By F. M. R. WALSHE, M.D., D.SC., F.R.C.P., F.R.S. Fifth Edition. Pp. xvi+351, with 59 illustrations. Edinburgh: E. & S. Livingstone Ltd. 1947. Price 16s. net.

This very remarkable book, first published in 1940, has now reached its fifth edition notwithstanding the tough times in which it has existed; surely a more effective tribute to its wide appeal than mere words of praise. With characteristic sagacity the author allows himself the comment in the preface that the book now emerges in more pleasing form from the "battledress" it has worn in the five years of its existence, a remark which means that the handicaps of austerity are now no more.

Certain changes in the text have been made to keep pace with the changes in knowledge and understanding of nervous disease, but the overriding intention of interpreting his speciality to practitioners and students is maintained. This, of course, means that most rarer and unusual conditions are omitted; but it may be said without overstatement that the book is unique and fills a most useful role, indeed without rival in the English language, in the purpose for which it is designed.

*The Acute Infectious Fevers.* By ALEXANDER JOE, D.SC., M.D., F.R.C.P.E., D.P.H., D.T.M. & H. Pp. 276, with 64 illustrations. London: J. & A. Churchill. 1947. Price 18s.

Dr Joe, whose wide experience in the care of infectious fevers and his many years as a teacher make him well qualified to write on this subject, gives a full and well-balanced account of the various infectious fevers, and the views expressed are largely coloured by his own experience. The illustrations have been well selected and have been excellently produced.

This little work should be of the greatest value to the student and practitioner alike.

*Improvised Equipment in the Home Care of the Sick.* By Lyla M. ALSON, R.N. Fourth Edition. Pp. xiv+265. Philadelphia and London: W. B. Saunders Company Ltd. 1947. Price 7s. 6d. net.

The nursing profession has long recognised the fact that good nursing care can only be given when the nurse possesses not only scientific knowledge and manual dexterity but also a warm understanding of the patient, his needs and his desires. In the fourth edition of this book Miss Alson has brought to the nursing profession up-to-date ideas on improvising articles to be used in caring for the sick. These should lessen the discomfort and hasten the recovery of the patient and give a greater feeling of confidence to the nurse.

*Blind Intubation and the Signs of Anaesthesia.* Third Edition. By J. U. HUMAN, M.R.C.S., L.R.C.P., D.A. Pp. x+230, with 61 figures. London: H. K. Lewis & Co. Ltd. 1947. Price 10s.

In this edition the author has expanded the contents of his original monograph on *Blind Intubation and the Signs of Anaesthesia* into a small handbook dealing with certain general aspects of anaesthesia. The material included is necessarily limited and whilst there are numerous points of practical interest expounded, it is doubtful whether the value of the original work has been enhanced by the additions made. Despite what appears to be a nonchalant disregard for syntax, the author's views, based on broad experience, are clearly stated and adequately illustrated.

*Practical Physiological Chemistry.* By P. B. HAWK, B. L. OSLER, and W. H. SUMMERSON. Twelfth Edition. Pp. xiv+1323, with 314 figures. London: J. & A. Churchill Ltd. 1947. Price 50s. net.

Hawk's *Physiological Chemistry* celebrates its twelfth edition and its fortieth birthday simultaneously with the senior author still in command. The ten years which have elapsed since the previous edition have produced great advances in Biochemistry including the rapid growth of Chemotherapy, the introduction of many new techniques dependent on electrical methods, the rapidly developing use of isotopes, and the identification of new vitamins and hormones. All of these subjects are adequately dealt with in the present edition.

The main part of the text deals with the accepted modern methods of biochemical analysis. This section has been enlarged, revised and brought up to date with the inclusion of the most recent and the most reliable procedures. The reader is given the choice of several methods for the determination of all the important constituents of blood and urine. In addition, there is much theoretical matter dealing with pure, physiological and pathological chemistry; and finally, there is a great mass of statistical data which adds much to its value as a book of reference.

The subject matter is brief and concise; the authors waste little space in their descriptions (which are always adequate) and they give abundant references to the original papers. Typographical errors are few, and the only surprising omission is that of the cerebrospinal fluid.

Every scientist who comes into contact with any branch of biochemistry will find that this book provides the answers to a multitude of questions.

*Chemical Methods in Clinical Medicine.* G. A. HARRISON, M.D. Third Edition. Pp. 630. London: J. & A. Churchill. 1947. Price 40s.

This new edition of Dr Harrison's standard work has been brought up to date and several new sections included. A most interesting one is that on pigmentation. The text is a clear exposition of method coloured by the valuable addition of the author's own comments and experience. A large number of practical methods are described which will be of great value to the student of clinical chemistry. The section on diabetes is a little disappointing. The results of the dietetic regimes outlined are clearly evident, but the diets are rather out of date and the danger is that the student reading this section, without any other knowledge, would consider that these illustrate the modern dietetic treatment of diabetes. More detail on the conduct of fat balances would have been very welcome. This is a book one can confidently recommend for the senior student or post-graduate student of medicine who realises the importance of bridging the link between clinical work and the laboratory.

*Surgical Note-Taking.* By CHARLES F. M. SAINT. Fourth Edition. Pp. viii+106. London: H. K. Lewis & Co. Ltd. 1947. Price 4s. 6d. net.

This excellent booklet is designed as a guide for surgical dressers commencing clinical studies. It describes in detail how to question a patient and examine the various systems in order to produce an efficient case record.

# BOOKS RECEIVED

- ALLEN, F. M. B., M.D., F.R.C.P. (LOND.). Aids to Diagnosis and Treatment of Diseases of Children. Eighth Edition. *(Ballière, Tindall & Cox, London)* 6s. net.
- BARBER, HUGH. The Occasion Fleeting. *(H. K. Lewis & Co. Ltd., London)* 15s. net.
- BEAUMONT, G. E., D.M.(OXON.), F.R.C.P. (LOND.), and PALMER, K. N. V., M.B. (CANTAB.), M.R.C.P. (LOND.). Practical Points in Penicillin Treatment. Second Edition. *(J. & A. Churchill Ltd., London)* 1s. 6d.
- BLACKIE, W. K., M.D., PH.D., F.R.C.P. (ED.), D.T.M. AND H. Malaria with special reference to The African Forms. *(Published for the Post-Graduate Press by The African Bookman, Cape Town)* 10s. 6d.
- BOYD, WILLIAM, M.D.DIPL., PSYCH. M.R.C.P. EDIN., F.R.C.P. LOND., LL.D. SASK., M.D. OSLO, F.R.S.C. A Text-Book of Pathology. Fifth Edition. *(Henry Kimpton, London)* 48s. net.
- CHAMBERLAIN, E. NOBLE, M.D., M.SC., F.R.C.P. Symptoms and Signs in Clinical Medicine. Fourth Edition. *(John Wright & Sons Ltd., Bristol)* 30s. net.
- CREW, F. A. E., M.D., D.SC., PH.D., F.R.S., F.R.C.P.ED. Genetics in relation to Clinical Medicine. *(Oliver and Boyd Ltd., Edinburgh)* 10s. net.
- DAS, K., M.B. (CAL.), F.R.C.S. (ENG. AND EDIN.) Clinical Methods in Surgery. *(The City Book Company, Calcutta)* 35s.
- GILMOUR, J. R., M.R.C.P. The Parathyroid Glands and Skeleton in Renal Disease. *(Geoffrey Cumberlege, Oxford University Press)* 18s. net.
- HADFIELD, GEOFFREY, M.D., F.R.C.P. (LOND.), and GARROD, LAWRENCE P., M.A., M.D., B.CH. (CAMB.), F.R.C.P. (LOND.). Recent Advances in Pathology. Fifth Edition. *(J. & A. Churchill Ltd., London)* 21s.
- HAGGARD, HOWARD W., M.D. Devils, Drugs, and Doctors. *(William Heinemann (Medical Books) Ltd., London)* 12s. 6d. net.
- HARRIS, D. T., M.D., D.SC., F.INST.P. Experimental Physiology for Medical Students. Fourth Edition. *(J. & A. Churchill Ltd., London)* 18s.
- ILLINGWORTH, C. F. W., C.B.E., M.D., CH.M., F.R.C.S.ED. A Short Text-Book of Surgery. Fourth Edition. *(J. & A. Churchill Ltd., London)* 30s.
- JAMIESON, E. B., M.D. Illustrations of Regional Anatomy. Sections 1-7. Seventh Edition. Bound volume. *(E. & S. Livingstone Ltd., Edinburgh)* 75s. net.
- LOVE, R. J. MCNEILL, M.S. (LOND.), F.R.C.S. (ENG.), F.A.C.S. The Appendix. *(H. K. Lewis & Co. Ltd., London)* 12s. 6d. net.
- MURRAY, IAN, M.D., F.R.F.P.S.G., F.R.C.P.E., and MUIR, MARGARET B., S.R.N. Good Health with Diabetes. *(E. & S. Livingstone Ltd., Edinburgh)* 2s.
- OGDON, J. A. HOWARD. The Kingdom of the Lost. *(John Lane, The Bodley Head Ltd., 8 Bury Place, London, W.C.1)* 10s. 6d. net.
- PANNETT, CHARLES AUBREY, B.SC., M.D., F.R.C.S. A Surgery Textbook for Students. Second Edition. *(Hodder and Stoughton Ltd., London)* 27s. 6d. net.
- PARKINSON, G. S., C.B.E., D.S.O., M.R.C.S., L.R.C.P., D.P.H., BRIG. R.A.M.C. (RET.), assisted by SHAW, KATHLEEN M., M.B.E. A Synopsis of Hygiene (Jameson and Parkinson). Ninth Edition. *(J. & A. Churchill Ltd., London)* 28s.
- PERCIVAL, G. H., M.D., PH.D., F.R.C.P.E., D.P.H., and TODDIE, ELIZABETH, S.R.N. Dermatology for Nurses. *(E. & S. Livingstone Ltd., Edinburgh)* 15s. net.
- ROBSON, J. M., M.D., D.SC. (LEEDS), F.R.S.E. Recent Advances in Sex and Reproductive Physiology. Third Edition. *(J. & A. Churchill Ltd., London)* 21s.
- Edited by RUNES, DAGOBERT D. The Selected Writings of Benjamin Rush. *(The Philosophical Library, Inc., New York)* \$5.00
- SWIET, JOHN DE, M.D. (LOND.), M.R.C.P. Essentials for Final Examinations in Medicine. Third Edition. *(J. & A. Churchill Ltd., London)* 9s.
- WOFINDEN, R. C., M.D., B.S., D.P.H., D.P.A. Health Services in England. *(John Wright & Sons Ltd., Bristol)* 10s.
- WOLFF, WERNER, Professor Psychology, Bard College. The Personality of the Pre-school Child: The Child's Search for His Self. *(William Heinemann (Medical Books) Ltd., London)* 25s. net.

# Edinburgh Medical Journal

October 1947

## THE CHLOROFORM CENTENARY EXHIBITION

4TH NOVEMBER 1947

By DOUGLAS GUTHRIE, M.D., F.R.C.S.E.

THE exhibition of relics relating to Sir James Young Simpson and his discovery of the anæsthetic value of chloroform attracted many visitors to the Upper Library Hall of Edinburgh during November 1947. Although the centenary of ether anæsthesia was the occasion of world-wide celebration in 1946, it was equally fitting and desirable that Edinburgh should honour the memory of one of her most eminent sons, and should mark the occasion of his discovery, on its hundredth birthday.

The celebration occupied the greater part of a memorable day. At daybreak three commemorative wreaths were placed at the base of Simpson's statue in Princes Street Gardens—from his relatives, from the Edinburgh Obstetric Society, and from the Scottish Society of Anæsthetists.

Then followed a Scientific Meeting at the University, devoted to the present-day use of chloroform as an anæsthetic. Professor A. R. Macintosh dealt with the design and construction of dosimetric inhalers, and traced the progress of apparatus for chloroform administration during the century of its existence. Dr John Gillies analysed an investigation into the current employment of chloroform by general practitioners and by specialist anæsthetists. Of 865 replies from the former class, 94 per cent. used chloroform in obstetrics. Dr D. S. Middleton related his experiences of chloroform anæsthesia in a Japanese prison camp, where many hundreds of operations were performed under chloroform with very few fatalities.

At the close of the meeting, Sir John Fraser, Principal and Vice-Chancellor of the University, conferred the Honorary Degree of Doctor of Laws upon Dr H. W. Featherstone of Birmingham, founder-president of the Association of Anæsthetists of Great Britain, and upon Sheriff T. B. Simpson, K.C., a grand-nephew of Sir J. Y. Simpson. A luncheon was held at the University in honour of the new laureates, and their health was proposed by Emeritus Professor R. W. Johnstone, whose speech is reprinted on pp. 534-9 of this issue.

In the afternoon there was a largely attended Reception at which Sir John and Lady Fraser welcomed the guests. Among many

distinguished visitors was at least one from overseas, Professor John Fulton, of Yale University, U.S.A.

An address on "James Young Simpson and Chloroform Anæsthesia" was delivered by Dr Douglas Guthrie, Lecturer on the History of Medicine. Dr Guthrie said that the present celebration detracted in no respect from the honour already paid to the American pioneers of anæsthesia by ether and nitrous oxide. Simpson's discovery was not only a further bold step in the line of progress; it marked the inauguration of anæsthesia as an exact science which, coupled with Lister's great discovery a few years later, effected a revolution in the practice of surgery and of obstetrics. Chloroform was essentially an Edinburgh product, and although it had now been outmoded to a large extent by other anæsthetic agents, it still had its place and was still widely used. Dr Guthrie gave a brief sketch of the life and work of Professor Simpson, one of the most versatile and enthusiastic of the many eminent figures in the history of the Edinburgh Medical School.

At the Reception, there was opened the exhibition of relics to which reference has been made, and, as no detailed account has appeared in print, it may be of interest to mention some of the more interesting items which were placed on view.

A large case was devoted to the apparatus used in chloroform administration. This ranged from the simple "rag and bottle" of former days to the complicated, but highly efficient, chromium plate and rubber machine of to-day. The intervening period was illustrated by the dosimetric inhalers of Snow, Vernon Harcourt and others, by numerous varieties of chloroform mask, and eventually by the Oxford inhaler, designed in 1942 for the use of paratroops. This section of the exhibition was arranged by Dr John Gillies from material largely supplied by Mr Charles King, London, who attended the Celebration.

The largest and most prominent of the exhibits was the dining-table at which Simpson and his assistants sat, on many evenings prior to that of 4th November 1847, engaged in the strange but heroic process of self-experiment. The table is now the property of the Church of Scotland, as also is Simpson's house at 52 Queen Street, now used as a centre for the training of Youth in Christian leadership.

Many personal relics of Simpson were included in the collection: photographs of his humble birthplace, of himself at various ages, of his terrier dog Puck, and of Lady Simpson's niece Agnes Petrie, the first woman to inhale chloroform. Other personal mementoes were Professor Simpson's silk top hat, of unusually large dimensions, his signet ring, his stethoscope, and an enamel brooch bearing his insignia, and the motto—*Victo dolore*. Apparently Simpson was wont to carry with him, as doubtless did many medical men, little tin japanned pocket cases containing pills and powders. Three of those were on view, and two of them were lettered, "Return to 52 Queen Street." It is significant that opium is prominent among the pills: *Pil. Opii*, *Pil. Plumbi c̄ Opio*, *Pil. Colocynth et Opio*, etc. The powders included, Dover's powder, Tartar Emetic, and Grey powder.

Of earlier Simpsoniana there was shown a schoolboy Essay on Herodotus, written when he was thirteen, and a copy of Pope's translation of *The Iliad*, given to him by his elder brother John when he left home, at the age of fourteen, to study at Edinburgh University. Some of his Class tickets have been preserved; of special interest are those of Robert Liston and of Alexander Monro, who were among his teachers. There was shown the exultant letter to his father-in-law: "I was this day elected Professor. My opponent had 16, and I had 17 votes."

As an example of his manifold activities, there was a scrap-book with a collection of replies to an enquiry, which he had personally addressed to fifty different hospitals, in an endeavour to compare the mortality of amputations without ether anæsthesia, with the mortality when ether was used. The letters are dated June and July 1847.

Another of Simpson's vigorous campaigns concerned his method of arresting hæmorrhage by the pressure of needles, so-called acupressure. By this means he hoped to obviate the use of the silk ligature, a fruitful source of sepsis. Lister, attacking the same problem from a different angle, had not then made his discovery. To illustrate acupressure, which Simpson regarded as an innovation of equal importance to chloroform anæsthesia, there were on view several of the needles employed, also a number of letters to surgeons in various parts of the country. "Have you the boldness to defy tradition and try the new method of Acupressure?" he writes to one of those correspondents.

Simpson's antiquarian interest is shown in a letter of David Laing, proposing an excursion to the Island of Inchcolm with a few antiquarian friends. He wrote, "I have engaged a steamer to leave Newhaven at  $\frac{1}{4}$  past three."

Perhaps the most interesting section of the exhibition was that directly concerned with chloroform. Among a number of prescriptions in Simpson's handwriting is one for a liniment, containing chloroform. The leather-covered drop bottle which Simpson constantly used was one of the most precious of the relics, and beside it was an original bottle containing chloroform prepared by Messrs Duncan and Flockhart in 1865. This firm of chemists had also lent two letters from a customer in Liverpool, a Miss Louise Melly, who wrote, in 1870, "I have been wishing much to do something for the wounded in this miserable war. . . . I saw that chloroform is very much needed, and I want you to send as much as you can for £10. I will send you the second half of the note when I know this has reached you safely." A subsequent letter, also preserved, accompanied the remainder of the £10 note. This method of sending money was frequently followed for reasons of security.

Simpson's reprint of his paper to the Edinburgh Medico-Chirurgical Society on 10th November, announcing his discovery, is entitled "Account of a New Anæsthetic Agent, as a substitute for Sulphuric Ether in Surgery and Midwifery." This publication, now rather rare,

was represented in the exhibition by two copies, one of which is a presentation copy with Simpson's signature. Almost of equal rarity is the "Answer to the Religious Objections advanced against the employment of anæsthetic agents in Midwifery and Surgery," also dated 1847. It is prefaced by the verse from The Epistle of James, Ch. IV, v. 17: "To him that knoweth to do good and doeth it not, to him it is sin." Simpson answered very effectively the critics who argued against any mitigation of heaven-sent pain, and who stated that it must be borne and not alleviated.

Of special interest is a letter, dated 8th December 1847, addressed to Professor Simpson by (Sir) William Laurence, surgeon to St Bartholomew's Hospital, who is sometimes said to have discovered chloroform anæsthesia before Simpson. He writes, "We tried Chloric Ether at St Bartholomew's, and found that it was not sufficiently powerful. As soon as we heard of chloroform we made trial of it. Mr Stanley used it on Nov. 20th in lithotomy and in amputation of the breast; I used it in two lithotomy cases on 20 and 27 Nov. . . . This range of experience has not afforded a single unpleasant result. I think that your department of practice will exhibit the powers of this new agent in the most striking point of view."

A description of the first use of chloroform for midwifery in London, by I. B. Brown, Accoucheur to Paddington Lying-in Charity, is contained in a reprint from *The Lancet* of 22nd January 1848.

Simpson's own first use of chloroform in midwifery was on 9th November 1847, five days after the discovery. A photograph of the young lady born on that occasion, taken at the age of seventeen, stood on Professor Simpson's table and was referred to by him as Saint Anæsthesia.

At least one of Simpson's biographers states that the baby was actually christened "Anæsthesia." Further enquiry revealed the fact that she was the daughter of a Dr Carstairs, presumably of Edinburgh, where the birth took place. A reproduction of the original photograph was placed on view among the other relics and was mentioned in a press report of the proceedings. A few days later a letter appeared in *The Scotsman* from the son of the so-called "Anæsthesia" Carstairs, who, he stated, had married his father in 1868, and who died in 1910. The name "Anæsthesia" was applied by Professor Simpson and by no one else. The lady was actually christened "Wilhelmina," on Christmas Day, 1847, and although she was born in Edinburgh she was the daughter of Dr William Carstairs, H.E.I.S., who, after his service in the East, was living in retirement at Cupar, Fife, where his father and grandfather had each been Town Clerk.

A further interesting fact was revealed in a letter from Dr R. O. Adamson of St Andrews, who mentioned that he possessed the original photograph, taken in 1860 by his father, Dr John Adamson, who practised for many years in St Andrews and who in 1840 took the first "calotype" photograph to be taken in Scotland.

No mention of Simpson's work is complete without a reference

to his assistants, Dr George Keith and Dr Matthews Duncan, the latter of whom became a distinguished obstetrician in London, who played so noteworthy a part in the discovery of chloroform anæsthesia. Several letters were on view, in which their names were mentioned.

Among Simpson's followers, much honour is due to Dr John Snow of London, the first to specialise in anæsthetics, who improved the technique of chloroform administration and rendered it safer, by his dosimetric method. Snow's book *On Chloroform and other Anæsthetics*, first published in 1858, is to-day one of the rarest prizes of the collector of early medical works. The copy, shown in the Exhibition, was from the University Library. A photograph of Dr Snow was beside it, and a letter from Snow to Simpson, dated from 54 Firth Street, London, on 28th April 1848, and stating, "I believe that chloroform is used in nearly all surgical operations in London."

Of course, Simpson did not discover the substance chloroform. Ether was known for three centuries before it was employed as an anæsthetic. The time-lag of chloroform was not so great. In 1831, Guthrie in America, Soubeiran in France, and Liebig in Germany, independently and almost simultaneously prepared chloroform. Priority should be accorded to Dr Samuel Guthrie, as he was several months in advance of the other two; a drawing of the still which he used in the preparation of his "sweet whisky" was alongside the chloroform exhibits. Guthrie's work has been recorded in a recent book by Dr J. R. Pawling, entitled, *Dr Samuel Guthrie, Discoverer of Chloroform* (New York, 1947).

The lighter aspect of Simpson's discovery was illustrated among the relics by a note in *Punch*, 1847, entitled "Chloroform at Billingsgate," and purporting to quote an announcement, "Oysters opened under the influence of chloroform; eels skinned under like circumstance, and know no more of having their coats taken off than an intoxicated husband." An amusing repercussion of the discovery, nearer its home, is exemplified in a play-bill of the Theatre Royal, Edinburgh, announcing "Doctor Chloroform's Establishment, or Pawnbroker's Shop." This play was one of the items of the Christmas Pantomime, and it ran until the end of January 1848.

The final item of the collection consisted of copies of the three best-known biographies of Sir J. Y. Simpson; by Rev. J. Duns, D.D., 1873, by Eve Blantyre Simpson (his daughter), 1896, and by H. Laing Gordon, 1897. Beside them was a copy of the first *Medical Directory for Scotland*, a tiny volume dated 1852, in which Simpson's name appears. It was not until 1861 that this publication joined forces with the *London and Provincial Medical Directory*, which had first appeared in 1851.

In his address Dr Guthrie thanked those who had lent the relics, in particular Sir J. Y. Simpson's granddaughters, Lady Willert and Mrs Beatrix Long, both of Oxford, and Mr Charles King of London, as well as Sheriff Simpson and other relatives of Sir James, now residing in Edinburgh.



## "SIR JAMES YOUNG SIMPSON AND CHLOROFORM" \*

By R. W. JOHNSTONE, C.B.E., M.A., M.D., F.R.C.S.E., F.R.C.O.G.

THE memory of any man great enough to deserve commemoration after the lapse of a century is usually celebrated around the time of his birth. But Sir James Simpson's fame is so inseparably bound up with his epoch-making discovery of the anæsthetic properties of chloroform, and the circumstances of the discovery on 4th November 1847 are so well-known, that it is altogether appropriate that we should honour his memory to-day—exactly one hundred years later.

The same inseparable association of the man and his discovery explains the wording of the toast. We might indeed adapt the epitaph which John Keats phrased for himself in the despondency of impending death and say that Simpson's name is "writ in chloroform." But when we keep in mind the dominant share which his discovery enabled him to take in bestowing upon mankind the transcendent mercy of anæsthesia, we might more suitably claim for him either or both of Horace's familiar lines—"exegi monumentum ære perennius" and "non omnis moriar."

I need not remind an Edinburgh audience that Simpson was first and last an obstetrician. I do not propose to speak of his contributions to midwifery or of his pioneer work in gynæcology further than to say here that the immense reputation which he had gained in these subjects before 1847 was an important element in what happened afterwards. But I would be acting discourteously were I to refrain from acknowledging the kindly propriety with which you, Vice-Chancellor, have associated our obstetricians with this celebration, and my own deep sense of the compliment you have paid to one who had the honour to stand for some years in the line of academic succession to Sir James Simpson in asking me to propose this toast.

In thinking of any epoch-making discovery beneficial to mankind it is interesting to speculate upon why the particular individual made the particular discovery at the particular time. In any such analysis one is likely to find a number of factors converging at a given point in time. Some would dismiss these as fortuitous. Others, amongst whom Simpson himself would assuredly be enrolled, would discern in them the workings of some providential purpose. To the childlike minds of the very devout the event might indeed appear as the direct gift of God. I remember hearing one such man, the late Dr J. W. Ballantyne, suggest that the discovery of anæsthesia was perhaps the reward granted for the great philanthropic advance made by the abolition of slavery. But if our more sophisticated minds hesitate

\* Toast given at a luncheon in Edinburgh University 4th November 1947.

to accept any such direct explanation, there still remains a field for speculation.

Why, then—James Young Simpson? If we look into his early history, we find that he was the seventh son of parents in humble circumstances in West Lothian. To speculate upon whether there is more in his being a seventh son than a mere indication of the virility and biological soundness of the stock from which he derived, would lead us into the obscurities of superstition, which throughout the ages have surrounded that "perfect number." He is said to have been a particularly bright, intelligent child, sensitive, loving and lovable, and old Scottish custom, aided doubtless in his case by some degree of superstition, decreed that the Benjamin should become the scholar of the family. I imagine that his home environment must have had much in it akin to the Scottish manse, whose sons have created something of a tradition in our land—the *res angusta domi*, the early training in self-reliance and in the superlative virtue of hard work, the disciplinary blessing of being a young member of a large family. Like many a son of the manse he came to this university as the dux of his village school and with the clear determination to make a great name for himself, but no clear idea of the particular sphere which he would ultimately elect to shine in. And like so many others he was led to his choice by what seemed at the time to be a very casual factor—the sharing of lodgings with two ambitious and diligent medical students. At any rate, after two years spent in the study of the classics and philosophy, he became a medical student, and in due course, after a creditable but not brilliant undergraduate career, he obtained his degree at the age of twenty. His M.D. thesis led to his appointment as assistant to Dr John Thomson, the Professor of Pathology, and Simpson himself regarded the training in accurate observation which he obtained in that post as a valuable formative influence in his life. Professor Thomson was the instrument of destiny in another way also, for he it was who advised Simpson to direct his special attention to midwifery.

By this time Simpson's early training in hard work had blossomed into that "transcendent capacity of taking trouble," which Carlyle named as one aspect of genius. He threw himself into the study of obstetrics with enormous energy and zeal, and in the extraordinarily brief period of six years a succession of original articles from his pen had won him a European reputation. His reward came in 1840 when Simpson, at the age of twenty-eight, was elected to the Chair of Midwifery by the Town Council in the teeth of the opposition of the Faculty of Medicine, one of whose greatest ornaments he was destined to become.

I doubt whether any impartial student of Simpson's antecedents and early life could find in them anything foreshadowing him as a man of destiny, whose work was to have a beneficent influence upon mankind for all time coming. But it was by this time obvious that he

was marked out for a professional career of exceptional brilliance. Chance or Providence, as you may prefer, had fashioned a man capable of being the suitable instrument.

Let us now look at the other questions—why chloroform, and why the particular time in history—and consider them together.

All that we know of Simpson's character warrants the postulate that he was not merely a sensitive man but a tender-hearted one, and we can well imagine the effect of the impact upon his mind of the sights and sounds of suffering alike in the operating theatre and in his daily life as an obstetrician.

To-day we are accustomed to operating theatres that have something in common with temples of healing—where in surroundings of immaculate cleanliness the white-robed surgeons and their acolytes perform their office with calm and deliberation. But the similarity stops there, for the patient, lying in secure and peaceful insensibility to sight and sound and touch, bears no semblance to the animal brought to the slaughter.

Before 1847 the scene was very different. I shall forbear to harrow your cupeptic feelings at this moment with any wealth of grizzly details. Suffice it to remind you that the patient, with all his natural apprehensions sharpened by terror and by the sight of the knife, was veritably like a lamb brought to the sacrificial table, upon which he had, perforce, to be strapped or held down. The sole contribution which the surgeon could make to the mitigation of the immediate suffering lay in the speed of his operating ; and in many cases the urgent necessity of achieving this, without any consequent loss of accuracy and dexterity, compelled him to steel himself against the unnerving appeal of his humane sentiments to a degree which reflected itself outwardly in an expression that, to the patient at least, seemed grim and relentless.

One picture may well be in the minds of many of you at this moment. It is a picture in which the ugly features have been omitted and the grim realities softened by the art of its tender-hearted author. But even so, the story of Ailie in Dr John Brown's little masterpiece, *Rab and his Friends*, remains a poignant one.

No sensitive medical student could fail to be horror-stricken by such scenes until such time as his feelings became sublimated into a desire to acquire the knowledge and skill that would enable him to save life even through the unavoidable infliction of temporary agony. Or, as Dr John Brown more simply put it—"until pity, as an *emotion* ending in itself, lessens—while pity, as a *motive*, is quickened and gains power and purpose."

And when Simpson had graduated through that ordeal, his destiny brought him into daily contact with the often prolonged suffering of the lying-in chamber. No simile for human suffering is more common in early literature than the pangs of the woman in travail. It is a small fact but one of profound significance that in every civilised language the word for "pain" is used as a synonym for the muscular efforts

by which the infant is expelled from the womb of its mother. It is true that after a natural labour the joy and the profound sense of fulfilment which the newborn child brings to its mother—the sense of beatitude that you may glimpse in some of the Madonnas of the old masters—does rapidly dispel her memory of the earlier anguish. But not all labours are natural, and difficult labours in those old days not merely deprived the mother only too often of the joy of a living child, but had in their circumstances everything, indeed more than everything, in common with a surgical operation. When I look back on my experience of midwifery, and try to imagine what it would have been without my having had the priceless privilege of being able—thanks to Sir James Simpson—to relieve the suffering by chloroform or some other anæsthetic, I feel appalled. It is easy to understand, therefore, how and why Simpson's mind, quickened by pity as a motive, was questing for some means to destroy pain. But that is not the whole story.

Surgery in the first half of the nineteenth century had been progressing. New operations were being devised and perfected, which of necessity in some cases took longer to perform than the older ones. Surgeons everywhere were under the intellectual and humanitarian urge to extend the range of their healing powers, and everywhere they found themselves baffled by two things—the problem of wound infection, which Pasteur and Lister were ultimately to solve, and the problem of pain. For there are limits to human endurance of pain, as recent years have only too well reminded us. The times were ripe for the discovery of anæsthesia. The world was waiting for an end to be put to the long years of neglect of nitrous oxide gas and of ether. Let us to-day remember and give all honour to the Americans who rescued first the one and then the other from the dubious environment of the night-clubs, where they were occasionally prostituted as intoxicants, and turned them to practical value in dentistry and surgery. The success of ether in particular was immediate, and Oliver Wendell Holmes, the Professor of Anatomy at Harvard as well as at the Breakfast Table, coined the new word "anæsthetic." When Simpson first heard the news from Boston, he wrote—"It is a glorious thought; I can think of naught else."

Some two months later, on 21st December 1846, the first surgical operation under ether on this side of the Atlantic was performed with complete success by Robert Liston in London. Liston was one of the most brilliant surgeons ever exported from Edinburgh, and he was an old friend of Simpson's. A few days later, Simpson, whose prodigious energy made him very "quick off the mark," went to London to get first-hand information. On his return he did something that was quite original—he tried out ether in childbirth—the first time in history that a general anæsthetic had been so applied. The results were successful but he was not satisfied, and Simpson with his two assistants, James Matthews Duncan and George Keith, pressed

forward in a feverish search for something better, which ultimately culminated in the dramatic scene at 52 Queen Street which we are to-day commemorating.

But if the battle against pain had been won, the battle against prejudice had only begun.

Such was Simpson's already established reputation that the news of his discovery spread like wildfire over the civilised world. And just as in the case of Jenner, of Semmelweiss, and later of Pasteur and Lister, so in the case of Simpson a great medical discovery aroused intense antagonism. The opposition came from two main quarters. Some members of the medical profession opposed it from a genuine fear that the abolition of pain would greatly increase the number of surgical operations, and consequently also their mortality. They were certainly right in their first claim but wrong in the second, and it was not very long before Simpson had collected reports from several famous hospitals which demonstrated that the blessing of chloroform had brought in its train the further blessing of a diminished mortality.

But a more subtle opposition came from the Pharisees of the day—the ultra-orthodox religious folk. These persons had comparatively little objection to anæsthesia for surgical operations, but they took the gravest exception to the relief of pain in childbirth. It was “unnatural” and contrary to the Scriptures. For had not God said to Eve “in sorrow thou shalt bring forth children”? One of these reverend enthusiasts for vicarious suffering even maintained that chloroform would “rob God of the deep earnest cries of women in labour”!

Simpson was always and in everything a doughty controversialist, but never, I think, did he reveal his powers to greater advantage than in dealing with these religious objectors. He met them on their own ground. He took them back to the original Hebrew of the Old Testament, and assailed them with the rapier of exegetical scholarship. Moreover, he tipped his weapon with a verse from the New Testament—St James's words “To him that knoweth to do good and doeth it not, to him it is sin”—which must surely have pierced the armour of his opponents. Finally, he gave the *coup-de-grace* by reminding them that God cast Adam into a deep sleep before the removal of the rib which became Eve—surely the first example of anæsthesia.

But fighting prejudice is rather like buffeting a feather-bed, and all the stuffing was not taken out of this particular bed until six years later. In 1853 Queen Victoria, who had borne seven children without anæsthesia, was given chloroform during the birth of Prince Leopold by Dr John Snow, the first man to specialise as an anæsthetist. Her Majesty allowed her appreciation to become known, and straightway her loving and loyal subjects accepted her august approval as full and conclusive justification of the use of this “impious innovation” in midwifery.

Simpson did not live to see the full fruition of the work of his great

junior colleague, Joseph Lister, which was the sublime complement to his own. And neither Simpson nor Lister, although the latter lived till 1912, could possibly have conceived of the vastness of the territory their combined work was opening up to modern surgery. Simpson, however, was under no illusion that chloroform was the last word in anæsthetics. He was not blind to its potential dangers, and he looked forward to something better. On this occasion it is pleasant to think that if his spirit can see the great advances which modern anæsthetists have made, it will indeed be a "blithe spirit."

I have the pleasure of coupling this toast with the names of Sheriff T. B. Simpson, K.C., and Dr Henry Featherstone, O.B.E. Having already spoken too long, and being quite unable to better the admirable remarks of the Dean of the Faculty of Law, I shall only say of these gentlemen, that, as distinguished representatives respectively of what I may call the Simpson "dynasty" in our midst and of the modern science of anæsthetics, they are worthily and happily chosen to respond to the toast of "Sir James Young Simpson and Chloroform" which I now ask you to honour.

# VAGOTOMY IN THE TREATMENT OF PEPTIC ULCER

By C. F. W. ILLINGWORTH and A. W. KAY\*

IN the treatment of peptic ulcer, whether by medical measures or conservative surgical operation, there are two main objectives—to reduce the acidity of the gastric juice and to put the ulcerated part at rest.

Since vagus stimulation is known (Pavlov, 1910) to bring about the secretion of the "appetite" juice and (Cannon and Washburn, 1912) to enhance the motor activity of the stomach, it seemed reasonable to suppose that these objectives might be attained by division of the vagus nerves.

The operation of vagotomy was introduced by Exner in 1914 for the relief of pain in the gastric crises of tabes and only recently has it been applied (Weinstein *et al.*, 1944; Dragstedt, 1945) in the treatment of peptic ulcer. The object of the present paper is to report the results in a small series in which the denervation was carried out by the abdominal approach.

*Surgical Anatomy.*—The vagus innervation of the stomach has been described in detail by McCrea (1926). In brief, the vagus fibres as they enter the abdomen through the œsophageal hiatus of the diaphragm are disposed in two main trunks or bundles, one anterior the other posterior. They may communicate in a plexus round the œsophago-gastric junction. From both bundles fibres pass down the lesser curvature and are distributed mainly to the fundus and body of the stomach. From the anterior bundle a distinct branch, the pyloro-hepatic nerve, passes to the right at a high level in the gastro-hepatic omentum and transmits fibres which reach the stomach along the right gastric and gastro-epiploic arteries. From the posterior bundle, branches pass to the cœliac ganglion and some of these may reach the stomach along the left gastric artery.

*Operative Technique.*—After division of the left coronary ligament and retraction of the left lobe of the liver, the vagus bundles are divided as they lie on the terminal part of the œsophagus. Since it is difficult to ensure division of all fibres at this point, in our series in addition, denervation was performed at a lower level by the method of Latarjet (1922). This comprises (1) division of the pyloro-hepatic branch as it lies in the gastro-hepatic omentum; (2) division of the main stem of the left gastric artery with its accompanying leash of nerves; this incision is carried down to the submucous coat of the stomach immediately below the cardia on the lesser curvature and

\* From the University of Glasgow and the Peptic Ulcer Clinic of the Western Infirmary, Glasgow.

extended for an inch or so over both surfaces of the stomach; (3) division of all nerve fibres accompanying the right gastric and gastro-epiploic arteries.

*Clinical Cases.*—Since the observations were of an experimental character, it seemed proper to restrict them to a small series of 6 cases. The patients were carefully selected. All had duodenal ulcer; in one there was also a gastric ulcer. All were men of similar ages, all gave a long history of severe indigestion which had resisted or relapsed after one or more periods of careful medical treatment in hospital. All were suffering, at the time of operation, from a severe and prolonged attack (see Table I).

*Methods of Investigation.*—In addition to a critical assessment of symptoms by repeated examination both before and after operation, the effect of denervation was studied by observations on the gastric motility and secretion.

TABLE I  
*Vagotomy for Peptic Ulcer*

Case.	Site of Ulcer.	Age.	Duration of Symptoms (Years).	Duration of Last Pre-operative Relapse (Months).
1	Duodenum	34	14	48
2	"	34	16	9
3	"	41	7	2
4	Stomach and duodenum	38	12	8
5	Duodenum	34	12	2
6	"	33	11	5

The gastric motility was studied by means of a balloon in the stomach connected with a tambour recording on a kymograph drum, following the technique described by Kay (1947). Records obtained in this way show that the stomach is normally in a state of tone, which remains constant with but small variations. In addition every two or three minutes the stomach undergoes contractions which show themselves as rhythmic waves lasting for perhaps twenty to thirty seconds. In the patient with active duodenal ulcer the tonus variations are more marked and there is a striking increase in the frequency amplitude and duration of the rhythmic contractions.

This was the picture in all 6 cases before operation. After operation there was a striking change, and gastrograms in all cases showed almost complete immobility, with only occasional slight alterations of tone to disturb the calm (Fig. (a)). In 4 cases the effect of parasympathetic stimulation by intravenous injection of 0.5 mgm. prostigmine was noted. Before operation this brought about a distinct increase in gastric motility, but after operation was without effect. We interpreted this finding as indicating that the denervation had been substantially complete.

The effect of vagotomy on the acid secretion, on the other hand,



was slight. In 3 cases there appeared to be some diminution in the volume of juice secreted, but the acid level was practically unchanged. This is in accord with expectation since the hormonal stimulation of acid remains unaffected. Unfortunately no record was made of the

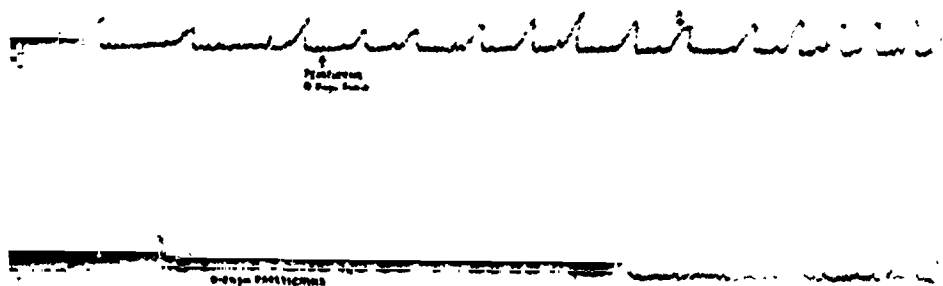


FIG.—Case 2. Gastric Motility (a) before (b) after vagotomy.

volume of night secretion which, according to Dragstedt *et al.* (1945, 1946), is notably reduced.

*Results.*—The immediate results appeared satisfactory, and all 6 patients experienced complete relief of the pain and indigestion

TABLE II  
*Vagotomy for Peptic Ulcer*  
Effect on Symptoms and Motility

Case.	Pre-operative.	Post-operative.				
		Two Weeks.	Six months.	One Year.	Eighteen Months.	Two Years.
1. Symptoms	++	—	—	—	—	++*
	++	—	—	+	++	++
2. Symptoms	++	—	—	—	—	—
	++	—	...	...	...	...
3. Symptoms	++	—	—	—	+	+
	++	—	—	+	++	...
4. Symptoms	++	—	++*	...	...	...
	++	—	+	...	...	...
5. Symptoms	++	—	—	—	—	—
	++	—	—	—	—	...
6. Symptoms	++	—	—	—	++*	...
	++	—	—	—	+	...

\* Gastrectomy performed.

from which they had suffered prior to operation. Even making full allowance for the tendency of peptic ulcer to undergo spontaneous remission it did seem that the vagotomy had been effective, and this appears to be confirmed by the fact that 5 of the patients remained symptom-free for eighteen months or more.

Unfortunately the relief did not prove permanent (Table II). One patient, the case with gastric as well as duodenal ulcer, suffered a relapse within three months; further operation showed that the gastric ulcer had penetrated the pancreas. Gastrectomy was performed and he has remained well since. Two others have required gastrectomy, having relapsed after eighteen months and two years respectively. A fourth patient relapsed after eighteen months but not severely. The remaining two continue symptom-free after three years.

Motility records (Fig. (b)) show that in each case the return of symptoms was preceded by return of motor activity and a positive response to prostigmine. These findings suggest that the recurrence was due to regeneration of the cut nerves. In two cases this was confirmed by microscopic examination after gastrectomy.

### DISCUSSION

The importance, in peptic ulcer, of following the results of treatment over a sufficiently long period before assessing its value is well illustrated in this series, in which the early results were promising but the final outcome quite unsatisfactory.

If we are correct in assuming that the recurrence of symptoms was due to regeneration, it must be concluded that there is no place for vagotomy by the abdominal route in the treatment of ulcer. If, as is possible, the recurrence of symptoms was due to inadequate denervation—some vagal fibres having been missed—the criticism remains that to perform a more complete denervation by the abdominal route would seem to be difficult of achievement and not always to be relied upon.

Although the end-results have been poor, from a broader standpoint the experience has been valuable in indicating the possibility of a different and more widely practicable approach to the ulcer problem. It will be noted that in 5 of our 6 cases prolonged healing of the ulcer, or at any rate prolonged relief of symptoms, was obtained by reducing the gastric motility although the acid level remained unchanged. A similar result may be obtained by the administration of drugs such as atropine, and there would seem to be a field in the future for a search for substances with a similar action but without harmful side effects.

### SUMMARY

In 6 cases of peptic ulcer treated by vagotomy by the abdominal route the immediate effect was to relieve all symptoms. Pain recurred in 1 case within three months, in 2 cases after eighteen months, and a fourth after twenty-seven months. Recurrence is attributed to regeneration of the cut nerves.

Vagotomy had a pronounced effect in reducing the gastric motility. It had no effect on the acid concentration of the gastric juice.

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## AN ANATOMICAL EVALUATION OF OPERATIONS FOR HYPERTENSION \*

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INCREASING attention is being devoted to operations for essential hypertension, and evidence is accumulating that they are of value in properly selected cases. Although the cause of this condition is uncertain, the main surgical attack has been directed against peripheral sympathetic structures, and in order to cover various ætiological possibilities a blunderbuss technique has been evolved requiring extensive autonomic ablations. No doubt more scientific methods will ultimately be evolved, such as the division of appropriate pathways within the cord or brain, but surgeons claim that present methods are justified by results. Sooner or later, however, medical advances should render all surgical treatment obsolete.

### THE RATIONALE UNDERLYING OPERATION

Different surgeons have differing ideas about what they wish to achieve, and these varying views are reflected in their operations. Nearly all wish to produce vasodilatation in the abdominal splanchnic area, and in addition most believe that a degree of somatic vasodilatation is desirable or even essential, particularly since Wilkins and Eichna (1941) have demonstrated that muscular, as well as cutaneous, vasomotor responses are under sympathetic control, and that reflex vasoconstriction in the limb muscles may be produced by cooling or by subjecting the individual to certain types of strain. Some authorities suggest that sympathectomy acts mainly by producing a passive relaxation of a sufficiently wide area of the vascular bed, with consequent decrease in the peripheral resistance. Others who subscribe to the neurogenic origin of hypertension and regard it as a manifestation of an exaggerated vasomotor response, ascribe importance to the actual denervation, while not denying that the result may be influenced by widespread vascular relaxation. The majority of surgeons wish further to interrupt sympathetic vaso-constrictor pathways to the kidney, in deference to the strongly supported view (Goldblatt, 1937) that renal ischæmia is in some way responsible for essential hypertension; incidentally, Trueta, Barclay, Daniel, Franklin and Prichard (1946) have demonstrated in a novel manner that ischæmia of the cortex may exist in a kidney that has a good medullary blood supply, an important observation with interesting implications. Suprarenal denervation is also regarded as essential in order to diminish the secretion of adrenaline,

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and it has been shown recently (Victor, 1945) that unilateral suprarenal ischæmia, like unilateral renal ischæmia, may be one cause of hypertension.

The following may be regarded as a consensus of opinion (Adson, Peet, Crile, Learmonth, Martin, White and Smithwick, Grimson) on the basic essentials in an operation for the relief of hypertension. The sympathetic supplies to the following should be divided :—

1. To the greater part of the abdominal splanchnic area—to produce widespread splanchnic vasodilatation.
2. To the vessels of the lower limbs—to produce somatic vasodilatation in these parts.
3. To the kidneys—to intercept possible reflex vasoconstrictor impulses.
4. To the suprarenals—to diminish the secretion of adrenaline and to prevent vaso-constriction of the suprarenal vessels.

These are regarded as the basic requirements, but other important considerations also influence the type of operation performed :—

1. It should carry the minimal risk to life, consistent with the production of the above results.
2. It should produce as few undesirable sequelæ as possible.
3. It should be sufficiently extensive to prevent nerve regeneration.
4. It should be pre- rather than post-ganglionic in type.
5. It should permit exploration of the renal, suprarenal and paravertebral areas through the wound used for sympathetic denervation, so that diseases or tumours in these regions may be excluded and biopsy material obtained for future study.

It is, of course, essential to remove sympathetic fibres and ganglia and not lymph vessels or nodes. Such mistakes have occurred; and anatomists who use micro-dissection methods soon discover that unless care is exercised nerve filaments and lymph vessels may be confused. One suspects that some of the fine structures and networks represented as autonomic nerves in the elaborate illustrations beautifying certain articles and monographs are in fact lymphatic vessels.

#### A GENERAL REVIEW OF THE TYPES OF OPERATION

Having decided what is required, the actual extent of the operation can be decided theoretically on anatomical and physiological grounds, although only the touchstone of experience can prove what is best, and no field of surgery reveals more clearly how surgical procedures are elaborated and remoulded in the light of experience and experiment. During the past thirty years many operations have been tried in hypertensive patients, and it is only by clinical trial and error that the basic requirements have been determined. The various operations which have pointed the way to those favoured at the present time

have been described and reviewed in many articles and monographs and this type of information need not be repeated here.\* It will suffice to mention that the operations may be classified into three broad groups :—

1. Operations on the coeliac plexus and/or suprarenal glands.
2. Division of spinal nerve roots.
3. Sympathectomies of varying magnitude.

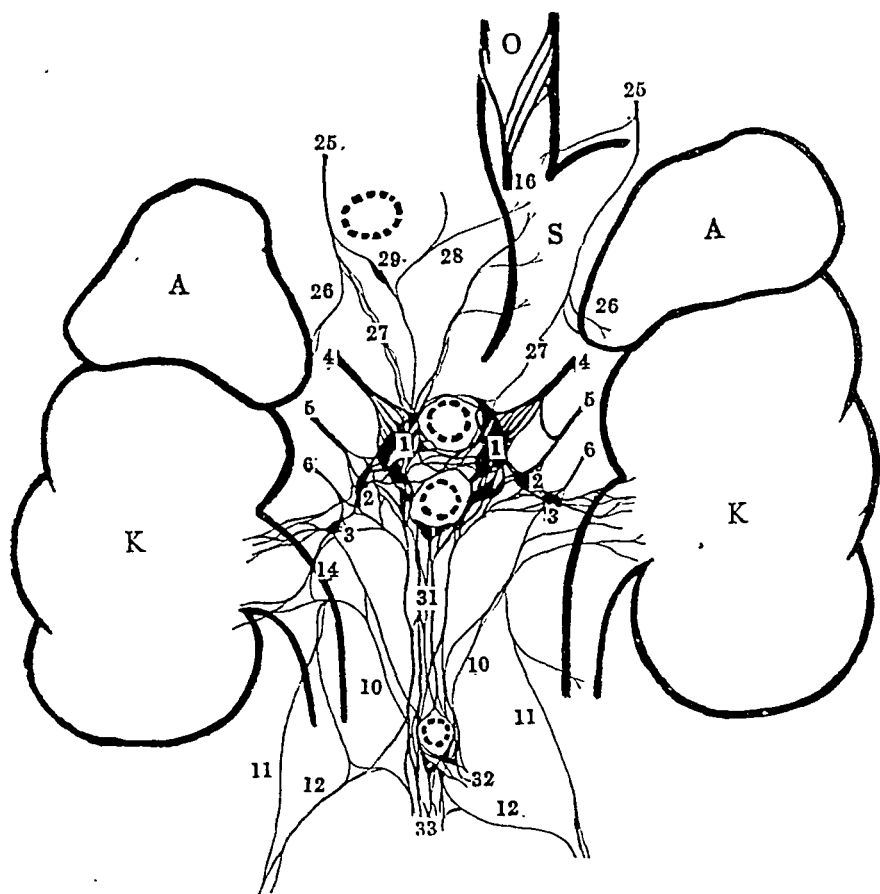


FIG. 2.—An outline diagram showing the average findings in a number of dissections. It shows interconnections between the phrenic nerves and coeliac plexus and between the renal plexuses and the spermatic and intermesenteric nerves. The branches of the anterior vagal trunk, the lumbar splanchnic nerves, etc., are not represented, and only the uppermost part of the stomach is indicated. The dotted circles represent respectively from above downwards the inferior vena cava, the coeliac artery, and the superior and inferior mesenteric arteries.

The great majority of surgeons now favour sympathectomy, and for various reasons the operations in the first two groups are less popular. Some of the objections are anatomical and the more important of these may be mentioned.

\* The list of references includes a number of articles containing descriptions and reviews of the more important operations.

Any operation involving partial or complete resection of the coeliac (solar) plexus is better avoided. Many synapses between pre- and post-ganglionic vasomotor neurones are contained within this plexus, and interruption of post-ganglionic fibres is now widely recognised as undesirable (Smithwick, Freeman and White, 1934; White, Okelberry and Whitelaw, 1936; Simmons and Sheehan, 1939). The suprarenal nerves are of necessity divided during coeliac ganglionectomy, but they have high powers of regeneration and a total and permanent

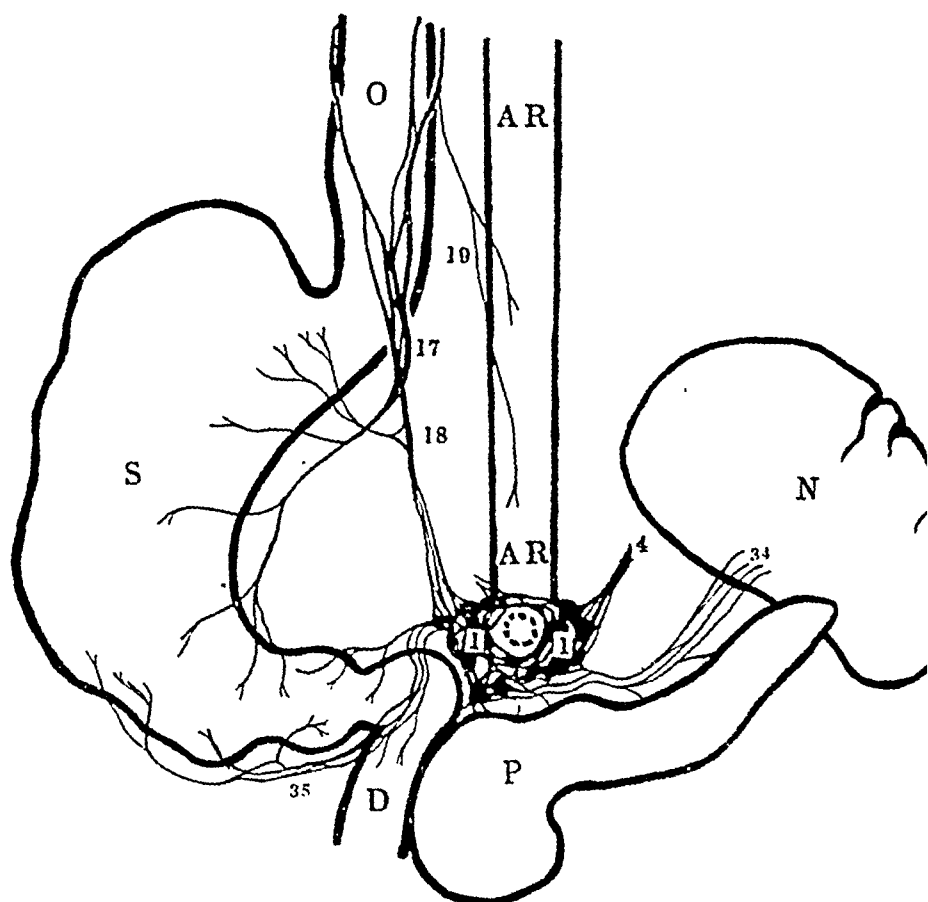


FIG. 5.—An outline drawing showing the average findings in a number of dissections. The stomach has been rotated to the right to expose the posterior vagal trunk and its branches, and some of the gastric, gastroduodenal, pancreatic and splenic branches of the coeliac plexus. The dotted circle represents the position of the coeliac artery.

suprarenal denervation is difficult to achieve. If the coeliac (semilunar) ganglia alone are removed, either partially or completely, the aorticorenal and renal ganglia will be left, and the lesser and least (lowest) splanchnic nerves which frequently terminate in them will escape division (Figs. 1, 2, 3 and 4). So also will the upper lumbar splanchnic nerves, and the contributions to the renal and suprarenal plexuses from the lumbar sympathetic chains, the aorticorenal and renal ganglia and the intermesenteric nerves (Mitchell, 1935*a*) (Figs. 1, 2, 3, 4 and 7). On the other hand even a partial coeliac ganglionectomy must destroy important parasympathetic contributions, since the coeliac branches

of the vagi become inextricably mixed in the coeliac plexus (McCrea, 1924; Mitchell, 1935<sup>b</sup> and 1940; Lannon and Weller, 1947) and could not be separated or spared during operations of this type (Fig. 5). Crile (1938) claims that by excising the coeliac ganglia regeneration of post-ganglionic fibres is rendered impossible, but this statement is only partially true, as it ignores the anatomical fact that the suprarenal innervation is peculiar, the preganglionic fibres passing through the coeliac plexus without interruption to end around the chromaffin cells of the suprarenal medulla. These medullary cells are derived from sympathochromaffin tissue which migrated outwards with the developing sympathetic nerves, and as they are analagous to post-ganglionic cells, removal of the coeliac ganglia does not destroy the suprarenal post-ganglionic neurones. Therefore on various grounds operations on the coeliac plexus fail to produce the effects now generally regarded as desirable.

Goldblatt (1937) has shown in animals that bilateral suprarenalectomy prevents the development of hypertension, or abolishes it when established. He has also shown that if any cortical tissue is left experimental hypertension may still be induced, even although the medullæ of both glands are completely destroyed. From the applied anatomical viewpoint total or subtotal removal of one or both suprarenal glands presents no great problems, but Goldblatt's findings show that a subtotal operation is not enough, and complete extirpation of vitally necessary tissue is better avoided!

Operations for hypertension involving extensive rhizotomies have never become popular, because the risk to life is not minimal, because they may interfere with the blood supply of the cord, and because they produce undesirable sequelæ such as paralysis of the abdominal parietal muscles, although this is said to produce less disturbance and disability than one would expect (Heuer, 1936). Severe criticism could not be levelled against these operations on purely anatomical grounds, but Leriche (quoted by Martin, 1938) described them as "debilitating and mutilating" and saw no point in "curing a disease by crippling the patient."

It has been found that sympathectomy alone, without coincident attacks on the somatic nerves or the suprarenal glands, can produce the desired results. Such procedures have largely replaced other types of operation for hypertension, but the optimum extent of the sympathectomy is still undecided. Every variant between simple renal or suprarenal denervation and so-called "total" sympathectomy has been tried, and one thing is certain—the more limited operations are useless. Attempts to denervate one suprarenal gland by division of the homolateral splanchnic nerves is valueless because each gland receives filaments from the upper lumbar sympathetic trunk of the same side, and possibly contributions from the corresponding phrenic nerve and from the opposite side of the coeliac plexus; while stripping of the respective renal or suprarenal vessels will produce at best only a



partial denervation (Mitchell, 1935*a*), a fact that may explain the different results obtained by different workers following allegedly complete visceral denervations. Even if complete renal denervation is accomplished there is no conclusive evidence that the renal blood flow is thereby increased (Grimson, 1941; White and Smithwick, 1944). Moreover these operations are too limited to prevent nerve regeneration, and in the case of the kidney they have the added disadvantage that they are post-ganglionic in type. All denervated vessels are abnormally sensitive to adrenaline (Smithwick, Freeman and White, 1934; Simeone, 1938), and if the claim of Schroeder and Steele (1940) that the arterioles of an ischæmic kidney are already supersensitive to adrenaline is substantiated, then renal denervation should aggravate rather than alleviate the condition, unless some effective means of greatly diminishing or suppressing the secretion of adrenaline is also employed. But if neurogenic factors are of ætiological importance in hypertension, then it may be argued that the abnormal arteriolar sensitivity is merely evidence in favour of the view that neurogenic changes always precede the renal ischæmia, thus producing what is tantamount to a partial renal denervation.

#### THE SYMPATHECTOMIES PRESENTLY FAVOURED

Clinical and experimental studies indicate that extensive sympathectomies are desirable, and it is now reasonably certain that the minimum necessary is bilateral extirpation of the lower portions of the thoracic sympathetic trunks and of the thoracic splanchnic nerves. This type of operation has been practised by Peet (1946) since 1933, with gratifying results in over fifteen hundred patients. He employs a supradiaphragmatic extrapleural approach and recommends bilateral extirpation of the lower thoracic sympathetic trunks, including the lowest three or four ganglia, and resection of 4 to 6 inches of the greater splanchnic nerves. The other thoracic splanchnic nerves are also divided, and if the lowest thoracic ganglia are difficult to reach he cuts their rami, even if this necessitates fairly extensive division of the vertebral attachments of the diaphragm.

The operation described by Allen and Adson (1940) is directed at a somewhat lower level. It consists of a sub-diaphragmatic division of the thoracic splanchnic nerves, removal of parts of the coeliac ganglia, and resection of the upper parts of both lumbar sympathetic trunks, including the first and second ganglia. For reasons already given the removal of nerves should be sufficiently extensive to prevent regeneration, and partial or complete removal of the coeliac ganglia is better avoided. Apart from these disadvantages, the Allen-Adson operation apparently satisfies the minimal requirements, as it too has been employed successfully in large numbers of cases.

It is doubtful, however, if in the surgical treatment of hypertension the minimum is the optimum, for there is reason to believe that by

increasing the extent of the denervation favourable results may be produced with greater certainty in a higher percentage of cases (White and Smithwick, 1944). Assuming that the premise about the basic essentials in operations for hypertension is correct, then more extensive procedures are necessary, and in 1940 Smithwick described an operation which he had practised since 1938 and which is virtually a combination of the Peet and Allen-Adson procedures, with the desirable omission of the partial coeliac ganglionectomy. He employs a combined supra- and infra-diaphragmatic approach and states that the operation can be carried out without difficulty by resecting the twelfth rib and by dividing the diaphragm between its lateral margin and the corresponding crus. He removes each sympathetic trunk from the ninth thoracic to the second lumbar ganglia inclusive, dividing all their intervening branches, and resects the greater splanchnic nerves from the mid-thoracic level to just above the coeliac plexus.

#### THE SUGGESTED OPTIMUM SYMPATHECTOMY

With the exception of the "total" sympathectomy described by Grimson (1941), Smithwick's operation is more extensive than any other commonly employed, yet it is not invariably successful in producing the desired results, and the Neurosurgical Service at Massachusetts is now attempting to assess the effects of extending the denervation upwards to the level of the fourth or fifth thoracic ganglia (personal communications from J. C. White). On anatomical grounds one believes that such an operation (removal of both sympathetic trunks from the fourth thoracic ganglia down to the second or third lumbar ganglia, plus bilateral resection of the greater, lesser and least thoracic splanchnic nerves (Fig. 7)) is the theoretical optimum, and that Grimson's "total" sympathectomy, producing undesired interference with ocular, cardiac, pulmonary and brachial sympathetic fibres, is needlessly extensive. Time, and the analysis of a sufficient number of careful records, will provide the ultimate answer, but in the meantime the anatomical reasons for favouring a more extensive operation will be given; there are, of course, other arguments based on clinical results (Scupham, de Takáts, van Dellen and Jesser, 1941; White, 1944) which one does not presume to assess.

Sympathetic nerves are more variable in their arrangement than somatic nerves, a circumstance that may be explained by the highly developed migratory powers possessed by the sympathochromaffin cells from which the autonomic nerves and plexuses are developed, and by the frequent and complicated plexiform arrangements which favour variations, since the same fibres have a choice of several alternative routes (Mitchell, 1935*a*). But macroscopic variations in the peripheral distribution do not necessarily indicate variation in the original source of the sympathetic supply to a particular viscus or vessel, any more than anomalies in the peripheral arrangements of

somatic nerves necessarily indicate variations in their root values. Nevertheless variations in peripheral distribution assume importance if it is desired to denervate a particular area or viscus, and they are of particular importance in sympathectomies because the escape of a few filaments may ruin partially or completely the effects of the whole operation. This has been explained on anatomical and physiological grounds. Only one unstriated muscle cell in about a hundred may possess a sympathetic nerve ending, but sympathetic effector responses depend on chemical mediation and the adrenaline-like substance liberated at the nerve endings may affect many adjacent cells, or even more distant structures, before it is inactivated. Denervated structures are hypersensitive to adrenaline, especially if the post-ganglionic fibres have been sectioned (Smithwick, Freeman and

## KEY TO ILLUSTRATIONS

1. Cœliac (semilunar) ganglion.
2. Aorticorenal ganglion.
3. Renal ganglion.
4. Greater (superior thoracic) splanchnic nerve.
5. Lesser (middle thoracic) splanchnic nerve.
6. Least (inferior thoracic) splanchnic nerve.
7. Loop connecting upper rootlet of greater splanchnic nerve to higher level of sympathetic trunk.
8. Lumbar splanchnic nerve(s).
9. Renal or suprarenal branch(es) from lumbar sympathetic trunk.
10. Communicating filaments between renal plexus and lower ends of intermesenteric nerves near commencement of inferior mesenteric plexus.
11. Superior spermatic nerve(s).
12. Middle spermatic nerve(s).
13. Inferior spermatic nerve(s).
14. Communication between renal plexus and superior spermatic nerve.
15. Communication between renal and gastroduodenal plexuses.
16. Anterior vagal trunk.
17. Posterior vagal trunk.
18. Cœliac branch of posterior vagal trunk.
19. Filament from œsophageal plexus passing downwards to aorta.
20. Aortic and œsophageal branches from sympathetic trunk or greater splanchnic nerve.
21. Thoracic cardiac branches of sympathetic trunk.
22. Pulmonary branches of sympathetic trunk.
23. Para-aortic nerve.
24. Para-aortic nerve attached to loop between stellate and second thoracic ganglia.
25. Phrenic nerve.
26. Branch from phrenic nerve or phrenic ganglion to suprarenal gland.
27. Communication between phrenic nerve and cœliac plexus.
28. Gastric and hepatic filaments arising from communication between right phrenic nerve and cœliac plexus.
29. Phrenic ganglion.
30. Communicating filaments between phrenic nerve and stellate ganglion.
31. Intermesenteric nerves (pre-aortic plexus).
32. Inferior mesenteric plexus.
33. Superior hypogastric plexus (pre-sacral nerve).
34. Splenic nerves.
35. Right gastro-epiploic nerves.

A—Suprarenal gland.  
 B—Bladder.  
 C—Colon.  
 D—Duodenum.  
 G—Gall bladder.  
 H—Liver.

K—Kidney.  
 L—Lung.  
 M—Diaphragm.  
 N—Spleen.  
 O—Œsophagus.  
 P—Pancreas.

S—Stomach.  
 T—Thoracic duct.  
 AR—Aorta.  
 AV—Azygos vein.  
 HV—Hemiazygos vein.



FIG. 1.—A dissection showing the coeliac, renal and superior hypogastric plexuses, the intermesenteric, suprarenal, spermatic, and some of the colonic nerves, a communicating branch between the right phrenic nerve and coeliac plexus, and the thoracic and lumbar splanchnic nerves.



FIG. 3.—A dissection showing the right sympathetic trunk and various branches, including thoracic and lumbar splanchnic nerves and contributions to the renal plexus. The upper root of the greater splanchnic nerve is connected by a loop to higher ganglia in the sympathetic trunk. The upper end of the right vagus nerve has been drawn to the right in order to display its various branches and others arising from the cervical sympathetic trunk. The viscera have been turned over towards the left side.

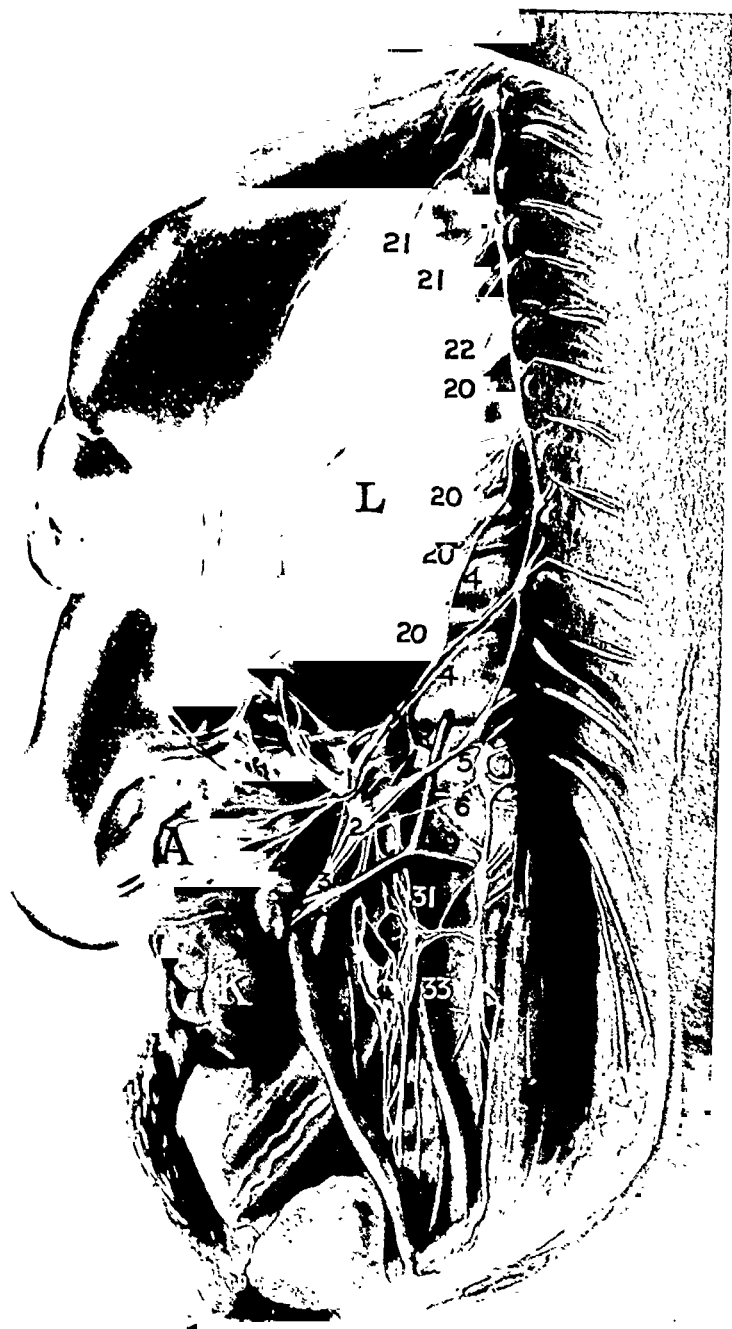


FIG. 4.—The viscera have been displaced towards the right side. The thoracic and lumbar parts of the left sympathetic trunk, various cardiac, pulmonary, aortic and œsophageal branches, the thoracic and lumbar splanchnic nerves, lumbar contributions to the renal plexus, and rami communicantes are all visible.

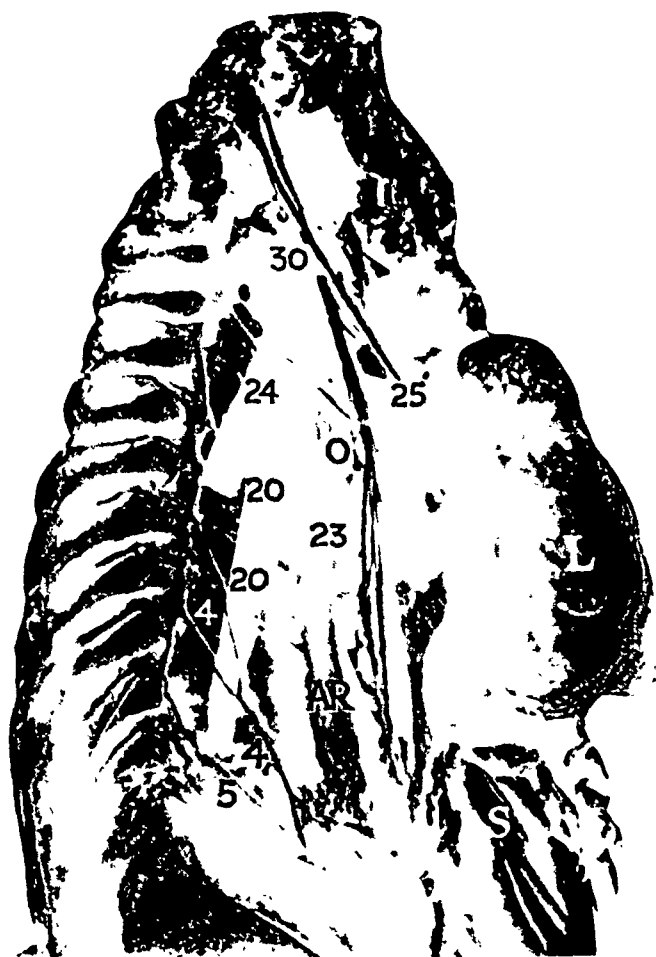


FIG. 6.—This specimen showed an unusually high attachment of the para-aortic nerve to a loop connecting the stellate and second thoracic ganglia. Various aortic, œsophageal, pulmonary and splanchnic branches of the sympathetic trunk are visible, and cardiac, pulmonary and œsophageal branches of the right vagus nerve. Two filaments can be seen connecting the right phrenic nerve and stellate ganglion.

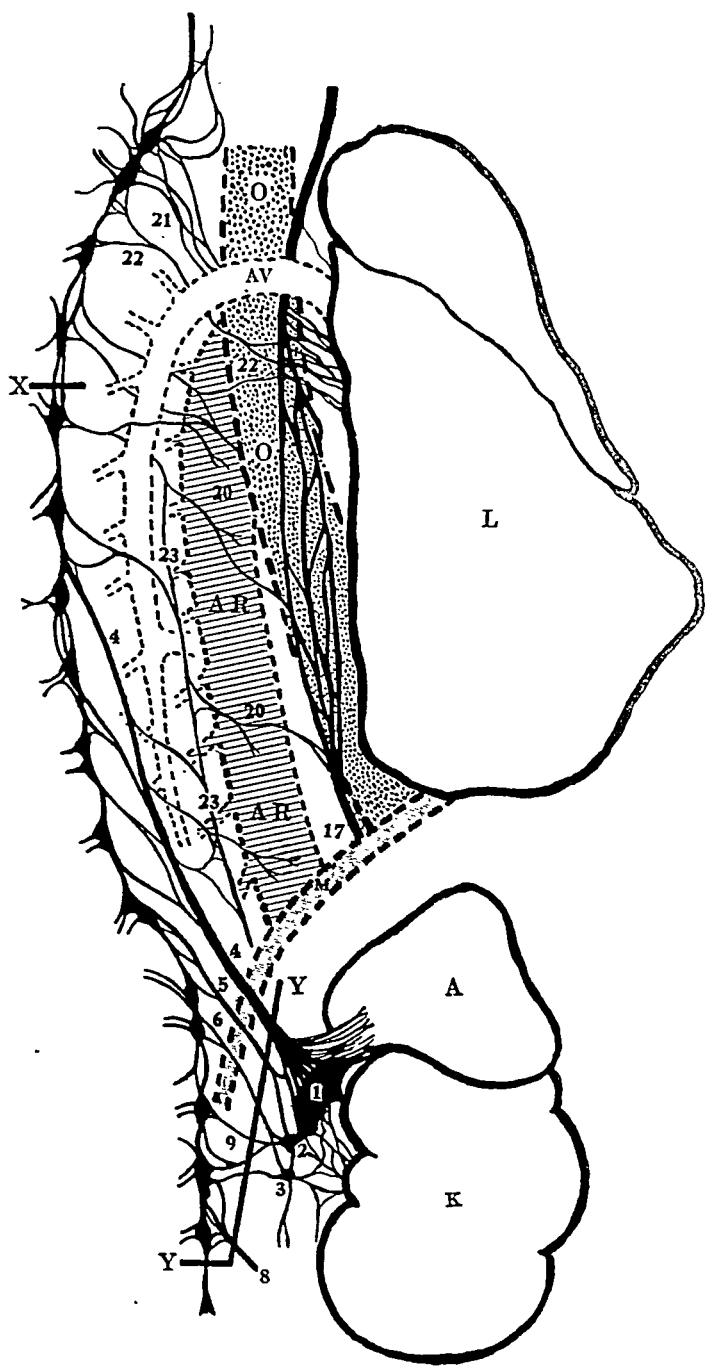


FIG. 7.—This diagram shows the suggested optimum extent of the sympathectomy in operations for hypertension. The sympathetic trunks and splanchnic nerves would be excised bilaterally between the points indicated by the lines X and Y.



White, 1934; Simeone, 1938), and thus the escape of only a small proportion of the nerve fibres supplying certain viscera or vessels may produce effects entirely disproportionate to their numbers. An exact knowledge of the anatomical arrangement is therefore essential in planning sympathectomies, and allowances must be made for possible variations. Most of the earlier failures in operations for hypertension were the result of too limited denervations, and it is probable that many of the failures in the more extensive procedures practised nowadays are due to the same cause. The surgeon believes he has divided all the fibres to a particular area, whereas several filaments may have escaped, and this apparently trivial omission may vitiate the whole procedure.

Resection of the lower thirds of the thoracic sympathetic gangliated trunks, including the lower three or four ganglia, and removal of the adjacent parts of the greater splanchnic nerves, will not interrupt all the sympathetic fibres passing from the thorax to the abdomen. The upper rootlets of the greater splanchnic nerves, which may be the largest both in regard to calibre and length, often arise as high as the sixth or seventh thoracic ganglia (Figs. 3, 4, 6 and 7). The main rootlets supply aortic and œsophageal filaments (Figs. 4, 6 and 7), some of which pass downwards to the abdomen, and these fibres arising from the uppermost rootlets will escape unless the greater splanchnic nerves are completely removed. Division of the trunks at the level of the sixth thoracic ganglia would ensure interruption of these filaments in most but not all cases. In 54 dissections one found that in 8 specimens rootlets of the greater splanchnic nerves arose at a still higher level, up to the level of the fourth thoracic, or even (one case) as high as the third thoracic ganglia. In another specimen (Fig. 3) the uppermost rootlet of the right greater splanchnic nerve was attached to the sixth thoracic ganglion, but it was connected by a loop to the fourth and fifth ganglia. It is almost certain, however, that in such cases division of the greater splanchnic rootlets at the same level as that recommended for the sympathetic trunk, *i.e.* between the third and fourth thoracic ganglia, would interrupt any abdominal fibres arising at or above that level; this should not increase the operative difficulties, because in this part of their course the trunk, rootlet and loop are not far apart.

Occasionally a para-aortic nerve is seen (Mitchell, 1938) formed by fine vertical strands interconnecting some of the pulmonary, aortic, œsophageal and lowest thoracic cardiac branches of the sympathetic trunks (Figs. 6 and 7), and in four out of five specimens its upper fibres arose as high as the fourth or fifth thoracic ganglia. This nerve has been seen only five times in over 50 dissections, but as more than half of these had been performed before it was first discovered, it may be more frequent than the figures suggest. So far it has not been detected on both sides in the same specimen. One case was of unusual interest (Fig. 6), because the nerve was attached

above to a loop connecting the first and second thoracic ganglia. It then ran down alongside the aorta, communicating en route with other filaments arising from lower ganglia in the thoracic chain, and it contributed a twig to the posterior part of the œsophageal plexus. This arrangement must be rare, since the area concerned has been subjected to intensive study by those interested in the nerve supply to the heart and the upper extremity, yet one can trace no record of any similar finding. To base an opinion, far less an operation, on a solitary observation is highly dangerous, so one adheres to the view previously expressed that in operations for hypertension resection of the sympathetic trunks as high as the fourth thoracic ganglia should prove adequate; if the nerve just described were common, then Grimson's "total" sympathectomy might be justified.

Still other autonomic fibres may reach the abdomen in the phrenic nerves, and it has been shown (Mitchell, 1940) that the left phrenic nerve sometimes supplies delicate filaments to the left suprarenal gland, the stomach and the coeliac plexus (Fig. 2), and that a slender branch derived from the right half of the coeliac plexus communicates freely with an offshoot of the right phrenic nerve before supplying filaments to the stomach and the liver (Mitchell, 1938) (Fig. 2). It is also possible to demonstrate filaments passing to the right suprarenal gland from the phrenic ganglion or from the terminal strand(s) connecting the phrenic nerve with the coeliac plexus (Figs. 1 and 2). The exact origin of these fibres has not been determined, and although they are probably sympathetic in nature, no proof of this is so far available. The phrenic nerve roots receive sympathetic fibres in the usual way through the corresponding rami communicantes, and on several occasions one has traced fine connections between a stellate ganglion and the phrenic nerve of the same side (Fig. 6). The possibility cannot be excluded that in these interchanges of fibres the phrenic nerves may be the donors rather than the recipients.

The œsophageal plexuses, which form the anterior and posterior vagal trunks, furnish another pathway for the transmission of autonomic fibres to the abdomen. They are mainly composed of parasympathetic elements, but communicate with the sympathetic trunks and splanchnic nerves, giving or receiving fibres via these channels. Both vagal trunks supply branches to the coeliac plexus, and that from the posterior trunk is substantial (Fig. 5). Another offshoot from the œsophageal plexus, arising about the mid-thoracic region, reaches the abdomen alongside the aorta (Fig. 5). All these branches may carry afferent or efferent sympathetic fibres, but it is likely that few, if any, would fail to be interrupted by section of the sympathetic trunks at the level of the fourth thoracic ganglia.

It is hardly necessary to say that sympathetic fibres pass downwards to the abdominal parietes along branches of the internal mammary artery and intercostal vessels and nerves, but there is no suggestion that these pathways are of importance in visceral innervation.

Consideration of the above evidence indicates that the complete interruption of all sympathetic fibres passing from the thorax to the abdomen in man is theoretically possible but practically impossible, unless one is prepared to subject the patient to unjustifiable risks and disabilities. The great majority of the sympathetic fibres, however, passing from the thorax to the abdomen, and all those considered to be of most importance in hypertensive operations (with the possible exception of minute suprarenal contributions from the phrenics), can be eliminated by bilateral removal of the splanchnic nerves and by extirpation of the thoracic sympathetic trunks as high as their fourth ganglia (Fig. 7). This, therefore, may be regarded as the optimal upper limit of the operation.

Granted that the premise about the basic essentials in operations for hypertension is correct, it can be stated on anatomical grounds that the lower limit of the operation should be as low as the second or even the third lumbar ganglia. Bilateral removal of the upper three lumbar ganglia ensures complete sympathetic denervation of the lower extremities and of the kidneys and suprarenals—assuming in the case of the viscera that the supradiaphragmatic part of the suggested operation has also been performed. Complete renal denervation is difficult to produce, and is unlikely to result from mere stripping of the afferent vessels, as the lower renal fibres derived from the distal ends of the intermesenteric nerves (pre-aortic plexus) near the origin of the inferior mesenteric plexus (Figs. 1 and 2) may remain untouched by this procedure (Mitchell, 1935*a*). Division of the splanchnic nerves, and of the renal or suprarenal nerves near the coeliac plexus, will miss these same lower renal fibres, and also the filaments which often pass to the kidneys and suprarenals from the first and second lumbar ganglia or the intervening portions of the sympathetic trunks (Figs. 1, 3 and 4). In addition definite connections exist between the renal plexus, the upper end of the testicular (spermatic) plexus and the nerves accompanying the gastroduodenal artery (Figs. 1 and 2). It is possible that sympathetic or parasympathetic fibres, or both, may select this pathway to reach the kidney from the coeliac plexus—and incidentally these connections between nerves supplying the stomach, duodenum, kidneys and testes may help to explain the peculiarly sickening effects of renal and testicular injuries.

Consideration of this evidence confirms the view that the lower limit of operations for hypertension should be at the level of the second lumbar ganglia, and if the surgeon wishes to make allowances for possible variations in the nerve supplies to the kidneys or lower extremities, he should also excise the third lumbar ganglia.

To recapitulate—if the premise about the basic essentials is accepted, on anatomical grounds the optimum extent of sympathectomy for hypertension is bilateral resection of the sympathetic trunks from the fourth thoracic to the third lumbar ganglia and removal of the splanchnic nerves (Fig. 7).

## THE BALANCE SHEET

On the credit side an operation of the extent indicated produces sympathetic denervation of the greater part of the abdominal splanchnic area and of the lower half of the body, and interrupts effectively the nerves to the kidneys and suprarenals. It is pre-ganglionic in type, and despite the high powers of regeneration possessed by these fibres (Tower and Richter, 1931; Grimson, Wilson and Phemister, 1937), it is sufficiently extensive to prevent regeneration, while it permits exploration of the renal and paravertebral areas.

On the debit side the operation carries a definite risk to life; it produces severe initial postural hypotension with vertigo which may be especially troublesome in the early post-operative period; it may lead to compensatory hyperhidrosis in the non-denervated areas; it interferes with ejaculation in the male owing to destruction of the upper lumbar ganglia; it is followed by a transient intestinal over-activity; the patients are more sensitive to changes in temperature; and it interrupts many afferent and efferent sympathetic fibres, which must result in some derangement, however ill-defined, of the bodily functions, and may mask symptoms and signs if some visceral disease supervenes.

The majority of these undesirable sequelæ become less evident in time, but they cannot be dismissed as of no consequence. Yet responsible surgeons and physicians, knowing all these possibilities, still find such operations justifiable. As a mere anatomist one is forced to assume that here we have another proof of the old adage that desperate diseases require desperate remedies.

## SUMMARY

1. The rationale underlying operations for hypertension is discussed briefly and the reputed basic essentials are enumerated.
2. The types of operation are reviewed in general terms and it is suggested that certain of the failures may be explained on anatomical grounds.
3. It is shown that the Peet, Allen-Adson and Smithwick procedures may not interrupt all the sympathetic fibres to the abdominal splanchnic area or to the kidneys and suprarenals.
4. Aortic and œsophageal filaments arising from the sympathetic trunks or splanchnic nerves above the levels of section, para-aortic nerves (when present), and sympathetic fibres in the phrenic nerves, œsophageal plexuses or vagal trunks may all reach the abdomen and may escape interruption in these sympathectomies.
5. Section at the level of the second lumbar ganglion may miss renal contributions arising from the sympathetic trunks below that level, and may not interrupt communicating fibres between the renal plexus and the superior spermatic, gastroduodenal or intermesenteric nerves.

6. Accepting the premise about the basic essentials as correct, on anatomical grounds it is suggested that the optimum sympathectomy for hypertension is bilateral resection of the sympathetic trunks from the fourth thoracic to the third lumbar ganglia and removal of the splanchnic nerves.

#### ACKNOWLEDGMENTS

I wish to thank Professor J. C. White of Harvard who first stimulated my interest in this problem, and Professor Geoffrey Jefferson who gave me the benefit of his invaluable advice. I wish also to thank Miss D. Davison, Medical Artist, Manchester University, for her fine drawing of the dissection shown in Fig. 4; and Mr Cain, Aberdeen University, and Mr Gooding, Manchester University, for their skilful photography. The expenses of the anatomical investigations were defrayed by the Medical Research Council.

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## AN APPARATUS FOR EXPEDITING ARTIFICIAL PNEUMOTHORAX REFILLS IN AN OUT-PATIENT CLINIC \*

By W. CHAMBERS, M.B., Ch.B., City Hospital, Aberdeen

THIS apparatus was devised in an attempt to expedite and facilitate the work of a large out-patient clinic.

Compressed air from a cylinder is led via a reduction valve and rubber tubing to one or more A.P. sets of Dr Duthie's pattern, being connected directly to the set in place of the hand bulb.

The essential part of the apparatus is a Coxeter reduction valve of constant pressure type, such as is fitted to the oxygen cylinder of a Boyle's anæsthetic machine. This valve allows air to pass at a constant predetermined pressure and cuts off the high pressure supply from the cylinder itself when air is not being used. There is thus no danger of the pressure building up beyond the predetermined level.

The adjusting screw on the valve is varied by experimentation until a suitable rate of flow is obtained. It has been found that an approximately "half-way" position results in a satisfactory rate to supply two A.P. sets via a Y connector.

The technique of refilling is unchanged except that no pumping by hand bulb is required. Turning the tap of the apparatus to "Patient" allows air to flow and displace fluid from one bottle to the other, while turning to the "Manometer" position allows intrapleural pressure readings to be obtained, and at the same time cuts off the supply of air.

This apparatus has been in use at Aberdeen for two years, and has proved completely satisfactory in facilitating the work of a large out-patient clinic.

\* Demonstration given at a meeting of the Tuberculosis Society of Scotland held in Aberdeen on 25th April 1947.



## SOME RESULTS IN THE TREATMENT OF LUPUS VULGARIS BY CALCIFEROL \*

By T. E. ANDERSON, M.D.

ALTHOUGH the early history of vitamin D is the history of rickets, cod liver oil has been used for many years in the treatment of tuberculous lesions, including those of lupus vulgaris. Stelwagon in 1907 mentions cod liver oil as one of the main standbys in the general treatment of lupus vulgaris—and he stresses general treatment. The salt-free diet of Gerson, later modified by Hermannsdorfer and Sauerbruch, gave excellent results in the treatment of lupus vulgaris when carried out accurately, but even that was admitted to be ineffective if the vitamin content were not kept high.

All forms of vitamin D so far investigated are derived from sterols, generally by photochemical reactions (Bicknell and Prescott, 1942).<sup>1</sup> Vitamin D<sub>2</sub>, or *Calciferol*, is made by exposing ergosterol (a sterol found only in plants, especially fungi) to the action of ultra-violet light; the only satisfactory way is to expose ergosterol in solution and the solvent is important, ether being the solvent of choice. Calciferol, if irradiation is prolonged, especially if the solvent is alcohol, turns to toxisterol (substance 248); the German preparation Vigantol contained chiefly toxisterol and was therefore highly toxic and had relatively little antirachitic effect. Vitamin D<sub>3</sub>, the naturally occurring vitamin, has 7-dehydrocholesterol (an animal sterol) as a provitamin, but is also formed by ultra-violet irradiation; the formation of the vitamin appears to occur on the skin rather than in it. Calciferol has the same antirachitic potency as vitamin D<sub>3</sub> in some animals, rather less in others, and is more toxic, possibly because it is generally contaminated with other products of the irradiation of ergosterol (lumisterol, tachysterol, toxisterol, suprasterol i and suprasterol ii).

*The mode of action* of calciferol is not known; an antibacterial effect is obtained by several substances with the phenanthrene ring (cholesterol, ergosterol, vitamin D), and even related phenanthrene substances such as bile salts have a bacteriostatic action on some micro-organisms (Raab, 1946). Certainly calciferol does not act by calcification, as histological examinations show. Vachon and Feroldi (1945), quoted by Dowling and Prosser Thomas, report persistence of lupomata in the scar tissue in all cases examined; in cases that appeared to be cured clinically the lesions were those of a cicatricial tuberculosis. Two cases followed histologically here do not give the same result; in another case one atypical tubercle was found in section three weeks after commencement of treatment.

*The toxic dose* of vitamin D is generally above 10,000 i.u. per pound of body weight (Reed, Struck and Steck, 1939),<sup>2</sup> but this does not mean that even smaller doses are safe (Bicknell and Prescott). Cases

\* Read at a meeting of the Tuberculosis Society of Scotland held in Aberdeen on 25th April 1947.

of renal damage and extensive calcification of soft tissues have been observed, although recovery took place within six months of cessation of calciferol administration. At least one fatal case has been recorded, however, in a child. The serum calcium level, in itself, is not a reliable guide to toxic effects, as some cases develop hypercalcaemia with little or no prodromal subjective symptoms and others develop toxic signs without elevation of the serum calcium. The subjective symptoms experienced by the patient are the most reliable guide, especially the feeling of increased well-being and appetite, which is one of the earliest signs of intoxication: soon this alters to headache, nausea, vomiting, polyuria, pains in the teeth, jaws and joints, paræsthesiæ and increased libido (Bicknell). Marked thirst is also a common sign and, in severe cases, diarrhœa may develop. Albuminuria may develop from renal damage and severe mental depression may come on with even lesser degrees of intoxication. Loss of weight is emphasised by some, in fact some state that this occurs in all cases on high dosage, but it has not been my experience that every case loses weight, in fact some have gained.

Bicknell and Prescott point out that a high intake of vitamin A or vitamin B<sub>1</sub> is said to decrease the toxicity of vitamin D and certainly vitamin B<sub>1</sub> has appeared to accelerate the disappearance of toxic symptoms in some cases here.

Calciferol in high, subtoxic doses has been used by many workers in diseases such as chronic arthritis, psoriasis, scleroderma, etc., but its first *use in lupus vulgaris* appears to have been in France by Charpy in 1941 (using Sterogyl-Roussel).<sup>3</sup> In this country Dowling and Prosser Thomas<sup>4</sup> commenced using high doses of calciferol at St Thomas's Hospital independently in 1943 and have published their results to date (1945, 1946). At present this treatment is being widely employed, and to-day I shall summarise the results I have had here since I commenced treating some cases in March 1946.

Reports are also appearing of its *use in other forms of tuberculosis*, e.g. by Wallace, 1946,<sup>5</sup> in the treatment of tuberculous glands and sinuses—some favourable results have been obtained (paralleled by the course of the adenitis in a few cases of lupus on treatment by calciferol here). But I need not emphasise that calciferol is a potent, toxic drug, and that careful supervision is necessary, especially in view of the Herxheimer reaction that occurs in the early stages of treatment, at least as far as skin and nodes are concerned (and therefore the possibility of temporary activation in other organs cannot be lightly set aside). The results have not been favourable in the few cases of pulmonary tuberculosis in which calciferol has been tried to my knowledge. Cardiovascular or renal disease are contra-indications to this type of treatment also.

In the past year 71 cases of lupus vulgaris (19 males and 52 females) have been started on subtoxic doses of calciferol at the Lupus Clinic at the Aberdeen Royal Infirmary. The cases have not been selected with regard to age or duration, extent or type of disease, in fact all

cases in which no definite contra-indication is found have been placed on this form of treatment as a routine.

The ages of the patients at the beginning of treatment ranged from 4 and  $\frac{2}{3}$  years to 81 years (average 44.2 years); the age at the onset of the disease varied from one month to 78 years (average 23.5 years), the duration of the disease ranging from one year to 50 years (average 19.2 years)—the discrepancy is due to lack of accurate record of age in a few cases.

Of the 71 cases 18 are either continuing treatment or are unable (for one reason or another, unconnected with calciferol) to attend or have defaulted during treatment and have not been traced, and one died—this case I should like to mention more fully later. In the remaining 52 cases a course of treatment has been completed and, although the period of observation is not more than six months after cessation of treatment, even in the first cases treated the initial results might be of interest.

In the 52 cases the *end-results* to date may be summarised as:—

Apparently cured . . . . .	41 (78.8 per cent.)
Greatly improved, but doubtful . . . . .	8 (15.4 " )
Not improved . . . . .	0 (0.0 " )
Apparently cured after full course of 6 months but relapsing and requiring further treatment . . . . .	3 (5.8 " )

In only 39 cases (75 per cent.), however, was calciferol used exclusively; in the remaining 13 (25 per cent.) some adjuvant treatment was employed (intradermal chaulmoogra oil esters, CO<sub>2</sub> snow contact U.V.R.-Kromayer Lamp), and I am tending to use more local treatment as time goes on, as results appear to be achieved more rapidly. The duration of calciferol treatment varied from 2½ months to 8 months (average 6.1 months) and was uninterrupted in 29 cases (55.8 per cent.), although the dose had to be reduced in some on account of toxic symptoms. In 23 cases (44.2 per cent.) treatment had to be suspended completely for a time in view of toxic symptoms.

I have used Dowling's dosage as a routine, namely 50,000 units three times a day orally where this is tolerated. In most cases this has been reduced to 100,000 units daily after three months, but in some 150,000 units have been administered daily for a full six months.

Serum calcium and phosphate estimations have been carried out at frequent intervals in most cases and never less than once every two months. In 15 cases (28.8 per cent.) levels of over 12 mgm per cent. have been recorded (up to 15.9 mgms. per cent.), in two cases without toxic symptoms. A rise of serum phosphate seems to be a more reliable pointer to early intoxication than the calcium level, but the patient's own symptoms are the most reliable guide, for, in all, 32 cases (61.5 per cent.) showed toxic symptoms (although in 13 of these had an increased serum calcium content). The serum calcium in the hypercalcæmic cases fell to normal in from two to six weeks.

The *toxic symptoms* noted were those recorded by others, namely

a temporary sense of excessive well-being, lassitude, headache, epigastric pain, marked thirst, loss of weight, conjunctivitis, synovitis, pains in the joints, sweet taste in the mouth, nausea, vomiting, giddiness, anorexia, loss of mental concentration, drowsiness, lower abdominal discomfort. The incidence of toxic effects and the severity are greater in the Aberdeen Clinic than Dowling records in his cases. (Is this a geographical affair—analogueous to differences in tolerance of neoarsphenamine?) In only one case, however, was calciferol not tolerated at all by mouth; in this case 300,000 units were administered intramuscularly every second day, without any upset.

I should like to mention in greater detail the only fatal case I have had among those taking calciferol; this case is not included among the 52 I have been discussing. The case is that of a male, 38 years of age, with extensive lupus of the face, nose, tongue and pharynx of over five years' duration. Calciferol treatment was started by 150,000 i.u. daily, but in a month hypercalcaemia developed (serum ca. 16.8 mgms. per cent.) with prostration, vomiting of anything (even water), conjunctivitis, pains in joints and tetanic twitchings. No Herxheimer flare occurred in the skin lesions, however. After an interval of about two months (by which time his serum calcium had been normal for some time and he felt perfectly fit and his lupus had improved greatly) calciferol was recommenced at a lower dosage (100,000 units daily), but about this time he reported swelling of an epididymis, which was obviously tuberculous in type. An epididymectomy was performed by Mr Michie, but a sinus persisted after operation, so calciferol was started again. By this time guinea-pig inoculation and pyelography had shown a tuberculous left kidney and, while removal was being considered, pyrexia developed and ultimately meningitic signs. The patient eventually died of tuberculous meningitis. At post-mortem examination no calcification of note was present except for some areas of the medulla of the infected kidney. Was the genito-urinary infection in this case precipitated by the calciferol treatment or does the case merely indicate that calciferol is useless (at least in relatively small doses given somewhat irregularly) in genito-urinary tuberculosis? Personally I am inclined to the latter interpretation, but even should the former be the truth, I feel that subtoxic doses of calciferol are justifiable in the treatment of a disease with such damaging physical and psychological effects as lupus vulgaris. The results to date are outstandingly superior to former methods of therapy and Dowling's observations appear to indicate that these results may be permanent.

<sup>1</sup> BICKNELL and PRESCOTT (1942), *The Vitamins in Medicine*, London, pp. 448, 449 and 495.

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<sup>3</sup> CHARPY, M. J. (1943), *Ann. Derm. Syph.*, Paris, 3, 331.

<sup>4</sup> DOWLING, G. B., and PROSSER THOMAS, E. W. (1945), *Proc. Roy. Soc. Med.*, 39, 2; also *Lancet*, 1946, 2, 919.

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# PROGNOSIS IN PULMONARY TUBERCULOSIS \*

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DR BRIAN THOMPSON published an article in *Tubercle* in 1942 which aroused considerable interest. This paper was based on observation of 406 bacteriologically proved cases of pulmonary tuberculosis diagnosed in County Durham during the years 1928 to 1938. Observation commenced at time of diagnosis, and all survivors were observed for at least three years, and a diminishing residue for increasing periods up to thirteen years from the date of diagnosis. In place of giving a mortality rate, he expressed his findings in terms of probability of survival as applied to a hypothetical 1000 patients. This is a method advocated by Bradford Hill and is very suitable for expressing chances

TABLE I  
*Probability of Survival of 1000 Patients in Life Table Form*

Year following Diagnosis. $x$	Probability of Surviving Each Year. $px$	Probability of Dying Each Year. $qx$	No. Alive on Each Anniversary out of 1000 Patients. $lx$	No. Dying Each Year. $dx$	Probability of Surviving a further 5 Years. $5px$
(1)	(2)	(3)	(4)	(5)	(6)
0	0.58	0.42	1000	420	0.25
1	0.72	0.28	580	162	0.36
2	0.86	0.14	418	59	0.46
3	0.83	0.17	359	61	0.48
4	0.83	0.17	298	51	0.52
5	0.85	0.15	247	37	0.50
6	0.92	0.08	210	17	...
7	0.89	0.11	193	21	...
8	0.90	0.10	172	17	...
9	0.86	0.14	155	22	...
10	...	...	123	...	...

of survival, which is just another way of recording mortality, in a chronic disease such as pulmonary tuberculosis.

Table I shows Thompson's results in "life table" form. It will be seen that out of 1000 hypothetical patients diagnosed at the same moment, and to whom the yearly survival rates of the patients in the series under discussion are applied, 580 would be expected to be alive on the first anniversary of diagnosis, 247 would be expected to be alive on the fifth anniversary and only 123 would be expected to be alive on the tenth anniversary of diagnosis. Moreover, at the time of diagnosis, the chance of a patient surviving for five years was 1 in 4, and should he reach the fifth anniversary of diagnosis his chance of surviving a further five years was 1 in 2.

\* Read at a meeting of the Tuberculosis Society of Scotland at Aberdeen, 25th April 1947.

The patients observed were living in an industrial area, and during much of the period under review suffered economic distress, but the author, who claimed that his figures were the most comprehensive then produced, was of the opinion that similar findings would be obtained in any industrial area.

There are three interesting features about these findings. In the first place, they have been widely accepted and quoted by various authorities including the Committee on Tuberculosis in War Time set up by the Medical Research Council. Secondly, they apply to patients from the time of diagnosis. There are numerous sanatoria which produce survival rates, but many such institutions only admit relatively hopeful cases and, moreover, their survival rates are calculated from the time of discharge of patients. In this way a rather more rosy picture of the fate of the tuberculous is produced than is warranted

TABLE II

*Probability of Survival of 1000 Patients in Life Table Form  
All Patients*

Year following Diagnosis. $x$	Probability of Surviving Each Year. $px$	Probability of Dying Each Year. $qx$	No. Alive on Each Anniversary out of 1000 Patients. $1x$	No. Dying Each Year. $dx$	Probability of Surviving a further 5 Years. $5px$
(1)	(2)	(3)	(4)	(5)	(6)
0	0.70	0.30	1000	300	0.45
1	0.88	0.12	700	84	0.60
2	0.89	0.11	616	68	0.63
3	0.91	0.09	548	49	0.67
4	0.90	0.10	499	50	0.68
5	0.93	0.07	449	31	0.66
6	0.92	0.08	418	33	...
7	0.94	0.06	385	23	...
8	0.93	0.07	362	25	...
9	0.88	0.12	337	40	...
10	...	...	297	...	...

by the true facts. Lastly, all patients included in Thompson's series had been proved bacteriologically to be suffering from tuberculosis. Clinical diagnosis is notoriously unsound and radiological appearances are so variable that in the absence of positive sputum, especially after the employment of such measures as culture and guinea-pig inoculation—material being obtained by gastric lavage or on a laryngeal mirror if necessary—skiagraphic shadows cannot be accepted as positive proof of the disease. Stocks found on analysing the survival rate of all patients notified as suffering from pulmonary tuberculosis in England and Wales during the years 1922 to 1939 that some 50 per cent. of them would be alive at the end of five years after diagnosis. Fishberg, presumably on American experience, makes a similar statement. In the light of Thompson's figures and those obtained for patients in the Aberdeen area, such a survival rate appears to be rather optimistic.

Experience in the tuberculosis services in this area, which has a relatively low incidence and death rate from the disease, suggested



that our patients had a rather better chance of survival than those in County Durham, and investigation confirmed this.

Between 1st January 1934 and 31st December 1943, 1257 bacteriologically proved cases of pulmonary tuberculosis were notified to the Regional Medical Officer of Health, 843 from the City of Aberdeen and 414 from Aberdeenshire. The necessary calculations having been made to ascertain the probability of survival for each year after diagnosis, the probability of survival of a hypothetical 1000 patients based on the rates experienced by Aberdeen patients is shown in Table II.

Since I propose showing you several of these tables, perhaps a diversion may be allowed to consider their construction. The table follows fairly closely the pattern of the national life-table drawn up by the Registrar-General, but in column (1) "year after diagnosis" replaces "years of age." Again, the first entry in column (4) is "1000 patients" in place of "100,000 infants" and column (6) is not found on the conventional life-table. The basis of the table is the value  $qx$  which is the probability of dying between the years  $x$  and  $x+1$ . The value  $px$  is the probability of surviving the year from  $x$  to  $x+1$ , and since a patient either lives or dies,  $p+q=1$ . The probability of survival having been worked out—it is the fraction resulting from dividing the number of patients alive at the end of the year by the number who were under observation at the beginning of the year—the other columns can be completed. The entry in column (6)  $5px$ , is the product of the probabilities of survival of five consecutive years, starting with that from which five years' survival is required.

It will be observed that in this instance, of the hypothetical patients, 700 would be alive on the first anniversary of diagnosis, 449 would be alive on the fifth anniversary and 297 would be alive on the tenth anniversary. At the time of diagnosis the chances of surviving for five years are just under 1 in 2, but at the end of five years the chances of surviving a further five are 2 in 3. You will recall that the numbers of Thompson's cases who would be alive on the first, fifth and tenth anniversaries of diagnosis were 580, 247 and 123 respectively, and the chances of surviving a further five years at time of diagnosis and on the fifth anniversary were 1 in 4 and 1 in 2 respectively. Thus, one would expect to have as many Aberdeen patients alive after two and a half years as would survive one year in Durham, and the number of Aberdeen patients who might be expected to be alive on the tenth anniversary of diagnosis exceeds the number of Durham patients who might be expected to be alive on their fifth anniversary.

#### SEX AND AGE AS FACTORS IN PROGNOSIS

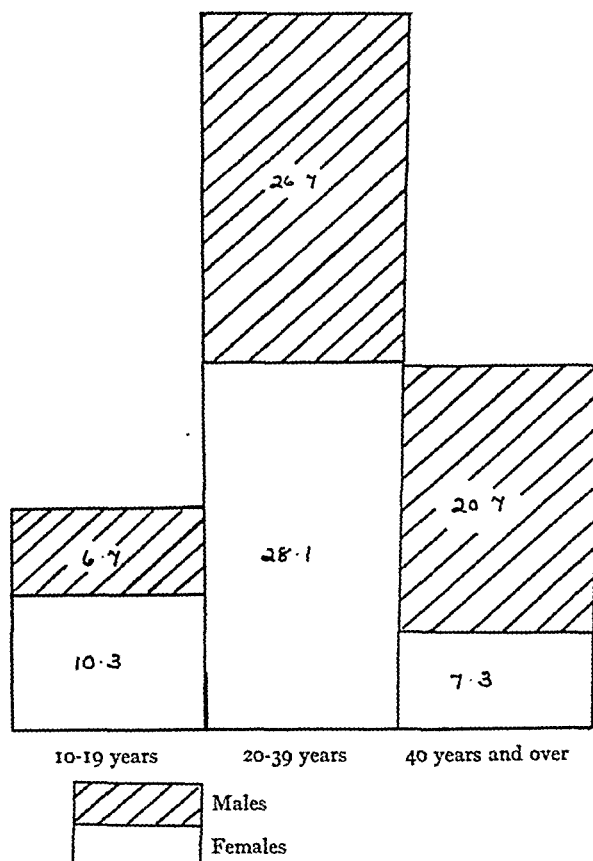
The 1257 patients comprised 681 males and 576 females. On comparison of survival rates, it was found that there was no significant

difference in the numbers of men and women alive on corresponding anniversaries of diagnosis.

The patients of either sex were subdivided, possibly rather arbitrarily into three age groups of 10 to 19 years, 20 to 39 years and 40 years and over. These three groups did seem to represent adolescent, mature, and from the treatment point of view at anyrate, the elderly patients. Table III gives a diagrammatic representation

TABLE III

*Diagrammatic Representation of Percentages of Males and Females in Age-Groups 10-19 Years, 20-39 Years, and 40 Years and over*



of the proportions of either sex in these three age groups. You will note that the percentages of males in each age group, commencing with the youngest, were 6.7, 26.7 and 20.7 respectively, and the percentages of females in each age group, again commencing with the youngest, were 10.3, 28.1, and 7.3 respectively. The greater proportion of females in the youngest group was not unexpected, but the size of the proportion of men in the oldest group, both in relation to females of the same age group and to males of the middle age group is rather surprising. Of the males in this group, 40 per cent. were in the 40 to

49 years age group, 31 per cent. were in the 50 to 59 years age group, and 24 per cent. were in the 60 to 69 years age group. The incidence is thus not too unevenly spread over a wide range of age.

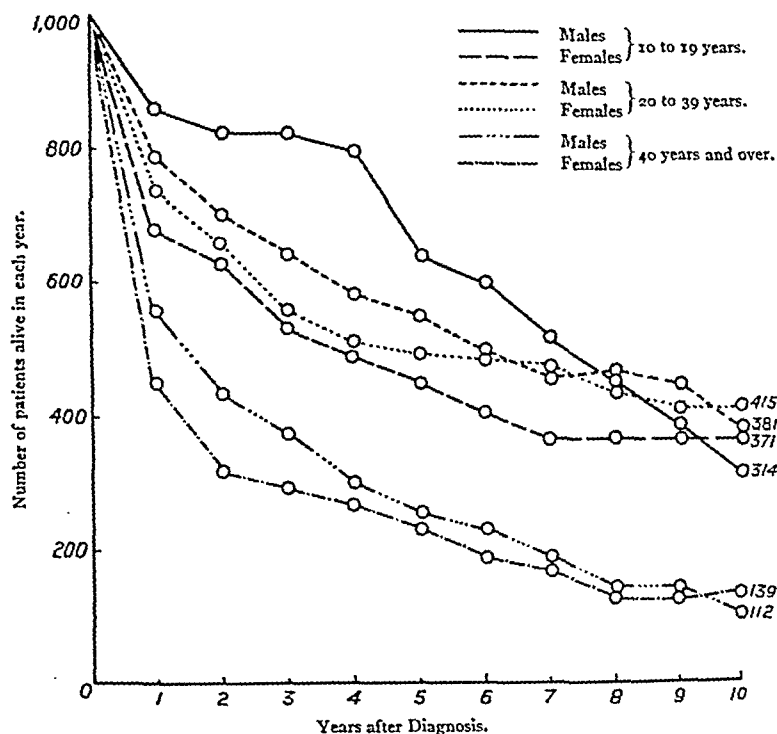
Comparison of the six "life-tables" prepared from the survival rates found for the six groups of patients showed that there was no significant difference in the survival rates between males in the 10 to 19 years group and the 20 to 39 years group, but males in both age groups had a statistically significant higher probability of survival up to two years after diagnosis than had those males in the oldest age group. Owing to the relative smallness of the numbers observed after the second anniversary of diagnosis the proportions in each group alive in subsequent years could not be compared on a statistical basis.

Similarly, with female patients there was no significant difference in the survival rates of those patients in the two younger age groups, but there was a statistically significant difference in these two age groups who would survive for two years when compared with the proportion of females aged 40 years and over who would survive for a similar length of time after diagnosis. It was found that in the 10 to 19 years age group, a greater proportion of males would be alive after one year from diagnosis than would females, but all other differences between the proportions of males and females alive on any anniversary of diagnosis in any of the age groups might well be due to chance.

The number of patients who would be expected to be alive on each anniversary for all six groups has been set out in graph form and this representation is seen in Graph 1. The poor survival rates of older patients, especially in the first year following diagnosis is clearly seen, and it would appear that the outlook for the older patient who develops phthisis is rather bleak. This is, of course, not the popular opinion of the profession with regard to tuberculosis in the elderly. In such people the disease is usually regarded as a chronic one—the theory of the grandparent with "chronic bronchitis" who infects the young children with tuberculosis dies hard. There is, too, little doubt that a number of patients can carry on fairly successfully for many years with active tuberculosis until the day when their resistance breaks down and they are forced to seek medical attention. In my view, however, the proportion of such patients is not large, nor, in my opinion, in this area at any rate is the number of older people who are only diagnosed as suffering from tuberculosis in their final illness. I grant that in a few instances, in accordance with the wishes of the ill person or his relatives, a patient may not be officially notified during life as a case of pulmonary tuberculosis, and only becomes known as such on receipt of a copy of the death certificate, but the number of such cases is small.

In considering the better survival enjoyed by males in the youngest age group, I hope to show later that the amount of lung tissue involved

and whether or not the patient is treated by collapse therapy are two factors which would appear to have influence on prognosis. Of these patients in the youngest age group, 75.4 per cent. of the females as against 52.2 per cent. of the males were classified as stage 3 of the Turban-Gerhardt system of classification: collapse therapy was employed in treating 40.2 per cent. of the males and 54.8 per cent. of the females. It would seem then, that one reason why the outlook is poorer for young girls than for boys is that at the time of diagnosis so many more of the girls suffer from advanced disease. Such a state is probably the result of the greater endocrine activity experienced



GRAPH 1.—Representation of probability of survival for a standard 1000 patients. Males and females in three age groups.

by the female sex in the years covered by this age group rather than to any difference in living conditions between the sexes at this time of their lives. In the other two age groups, differences in proportions in the numbers in each stage of classification and the numbers treated by collapse of the lungs were slight.

#### INFLUENCE OF COLLAPSE THERAPY ON PROGNOSIS

Of the patients in the series, no fewer than 399 or 31.7 per cent. of the total underwent some form of collapse therapy.

Artificial pneumothorax was induced in 354 patients, which is 88.7 per cent. of those treated in this way, and 45 patients had some-

other form of collapse measure—21 had phrenic interruption, 19 had thoracoplasty and 5 had pneumoperitoneum. There were 58 patients whose pneumothorax was abandoned in favour of some other form of treatment, or supplemented by it, and of these patients 13 had phrenic interruption, 17 had thoracoplasty and 13 had pneumoperitoneum. You will note, that in 296 patients or 74·4 per cent. of all who were treated by collapse methods, artificial pneumothorax was the method of choice. Table IV is the "life-table" based on survival rates calculated for this group of patients. Of the 1000 hypothetical patients, no fewer than 920 would be alive at the end of the first year, 680 would be alive at the end of the fifth year following diagnosis and 502 would be alive ten years after diagnosis. At the time of diagnosis the chances of surviving a further five years are greater than 2 in 3, and if the first five years are survived, the chances of surviving a further five

TABLE IV

*Probability of Survival of 1000 Patients in Life Table Form  
Patients treated by Collapse Therapy*

Year following Diagnosis. $x$	Probability of Surviving Each Year. $fx$	Probability of Dying Each Year. $gx$	No. Alive on Each Anniversary out of 1000 Patients. $lx$	No. Dying Each Year. $dx$	Probability of Surviving a further 5 Years. $5fx$
(1)	(2)	(3)	(4)	(5)	(6)
0	0·92	0·08	1000	80	0·68
1	0·94	0·06	920	56	0·70
2	0·91	0·09	864	78	0·67
3	0·94	0·06	786	47	0·70
4	0·92	0·08	739	59	0·68
5	0·95	0·05	680	34	0·73
6	0·90	0·10	646	65	...
7	0·95	0·05	581	29	...
8	0·91	0·09	552	50	...
9	1·0	0·0	502	0	...
10	...	...	502	...	...

years are almost 3 in 4. Comparison of this table with Table II, which is based on data pertaining to all patients in the series, shows that of the collapse therapy group the proportion alive on each anniversary of diagnosis up to the seventh is significantly greater than the proportions of the whole series alive on corresponding anniversaries of diagnosis. Of the 396 patients, 15 were in stage 1 and 62 in stage 2 of the classification.

#### EXTENT OF DISEASE

At the time of diagnosis, the patients were classed in one of the stages of the Turban-Gerhardt system of classification. In this classification, stage 1 comprises patients with infiltration in the apex of one or both lungs, or a small part of one lobe, with no marked toxæmia. Stage 2 comprises patients with infiltration amounting to half a lobe, no cavitation and but moderate toxæmia. Stage 3 comprises patients who have infiltration of one or more lobes, cavitation and

serious toxæmia. The classification of 42 or 3·3 per cent. of the patients was unknown, but of the 1215 patients whose classification was known, 9·3 per cent. were classed as stage 1, 14·9 per cent. were classed as stage 2 and 75·9 per cent. were classed as stage 3. In view of the relative paucity of patients classed as stage 1 and stage 2 and since cavitation and serious toxæmia should not have been present in these patients, the two groups were combined, and the "life-table" based on the survival rates of these 294 patients is shown as Table V. Of the 1000 hypothetical patients in this instance, 920 would be alive a year after diagnosis, 724 would be alive after five years and 548 would be alive after ten years. At the time of diagnosis, the chances of surviving for a further five years were just under 3 in 4, and on the fifth anniversary of diagnosis the chances of surviving a further five years are just better than 3 in 4. These survival rates are much

TABLE V  
*Probability of Survival of 1000 Patients in Life Table Form. Patients in Stages 1 and 2 of Turban-Gerhardt Classification*

Year following Diagnosis. $x$	Probability of Surviving Each Year. $p_x$	Probability of Dying Each Year. $q_x$	No. Alive on Each Anniversary out of 1000 Patients. $l_x$	No. Dying Each Year. $d_x$	Probability of Surviving a further 5 Years. ${}_5p_x$
(1)	(2)	(3)	(4)	(5)	(6)
0	0·92	0·08	1000	80	0·72
1	0·96	0·04	920	37	0·74
2	0·95	0·05	883	44	0·70
3	0·96	0·04	839	34	0·70
4	0·90	0·10	805	81	0·68
5	0·94	0·06	724	43	0·76
6	0·91	0·09	681	61	...
7	0·94	0·06	620	37	...
8	0·94	0·06	583	35	...
9	1·0	0·0	548	0	...
10	...	...	548	...	...

better than those for the series as a whole, but not very much better than those for patients treated by collapse therapy.

The "life-table" based on the survival rates of the 921 patients classed as stage 3 is shown in Table VI. At the end of one year after diagnosis only 630 would be alive. At the end of five years 360 would be alive and after ten years only 191 would survive. At the time of diagnosis the chances of surviving for five years were just better than 1 in 3, whilst if five years were survived the chances of surviving a further five years were slightly better than 1 in 2.

These rates of survival are very poor when compared with those in the combined group comprising patients classed in stages 1 and 2. Of the latter, more patients would be alive after six and a half years than the number of patients classed as stage 3 who would survive for one year, and more of the patients in the milder disease group would survive ten years than would survive two years if in the other group.

Whilst it is perhaps too obvious to state that the earlier cases have, on the whole, a better prognosis, it is perhaps not realised just how great is the difference in the chances of survival of the patients diagnosed early in the course of their illness. In these last two tables, the number

TABLE VI  
*Probability of Survival of 1000 Patients in Life Table Form  
Patients in Stage 3 of Turban-Gerhardt Classification*

Year following Diagnosis. $x$	Probability of Surviving Each Year. $px$	Probability of Dying Each Year. $qx$	No. Alive on Each Anniversary out of 1000 Patients. $1x$	No. Dying Each Year. $dx$	Probability of Surviving a further 5 Years. $5px$
(1)	(2)	(3)	(4)	(5)	(6)
0	0.63	0.37	1000	370	0.36
1	0.84	0.16	630	101	0.53
2	0.87	0.13	529	69	0.57
3	0.87	0.13	460	60	0.62
4	0.90	0.10	400	40	0.65
5	0.91	0.09	360	32	0.53
6	0.92	0.08	328	26	...
7	0.95	0.05	302	15	...
8	0.91	0.09	287	26	...
9	0.73	0.27	261	70	...
10	...	...	191	...	...

of survivors in the combined group of patients classed as stage 1 and stage 2 is significantly greater than the number of survivors classed as stage 3 on corresponding anniversaries of diagnosis up to the ninth. Regarding age as a factor, 18.7 per cent. of the patients in the combined

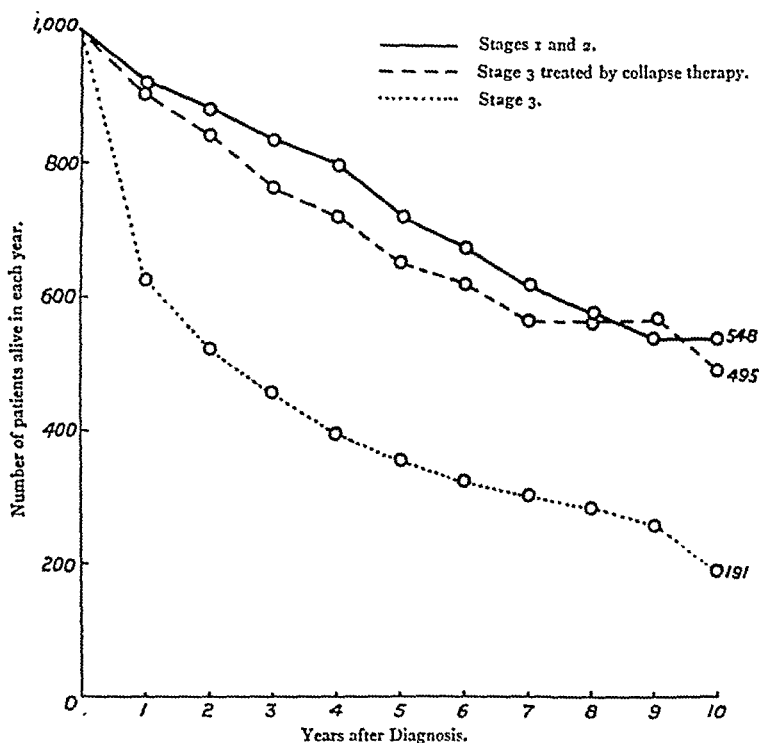
TABLE VII  
*Probability of Survival of 1000 Patients in Life Table Form  
Patients in Stage 3 treated by Collapse Therapy*

Year following Diagnosis. $x$	Probability of Surviving Each Year. $px$	Probability of Dying Each Year. $qx$	No. Alive on Each Anniversary out of 1000 Patients. $1x$	No. Dying Each Year. $dx$	Probability of Surviving a further 5 Years. $5px$
(1)	(2)	(3)	(4)	(5)	(6)
0	0.92	0.08	1000	80	0.66
1	0.92	0.08	920	74	0.68
2	0.91	0.09	846	76	0.68
3	0.94	0.06	770	46	0.75
4	0.91	0.09	724	65	0.79
5	0.95	0.05	659	33	0.75
6	0.92	0.08	626	50	...
7	1.0	0.0	576	0	...
8	1.0	0.0	576	0	...
9	0.86	0.14	576	81	...
10	...	...	495	...	...

group and 30.5 of the stage 3 group of patients were forty years of age or over. This is not a very great difference in age composition and is not likely to have influenced the results to any great extent.

No fewer than 319 or 34.6 per cent. of the 921 patients classed as stage 3 were treated by collapse therapy. Table VII is the "life-

table" based on the survival rates of these patients. Of the hypothetical 1000, the numbers who would be alive on the first, fifth and tenth anniversaries of diagnosis are 920, 659 and 495 respectively. At the time of diagnosis the chances of surviving five years were 2 in 3, and on the fifth anniversary the chances of surviving a further five years were 3 in 4. Age of patients may have had a more marked influence on these results. Of the 921 patients classed as stage 3, 30.5 per cent. of them were aged forty years or over, but of those treated by collapse methods only 7.5 per cent. were of this age group.



GRAPH 2.—Representation of probability of survival for a standard 1000 patients. Patients in stages 1 and 2 and stage 3 of Turban-Gerhardt classification and patients in stage 3 treated by collapse therapy.

Even so, in my view, the method of treatment was by far the more important factor.

These survival rates are almost identical with those based on the survival rates of the collapse therapy group of the whole series. Indeed, apart from 80 patients in stages 1 and 2, they are the same group of patients. The figures show, I think, that even the patients found at the time of diagnosis to have disease sufficiently advanced to allow of classification in stage 3, which, I admit, is too comprehensive, and if they are suitable for treatment by collapse of the lung, they may enjoy a survival rate not very far removed from those patients classed in stages 1 and 2.

Graph 2 is a representation of the survival rates of patients in the



combined stages 1 and 2, those in stage 3, and those in stage 3 treated by collapse therapy.

You will recall that in 74·4 per cent. of the patients treated by some form of collapse therapy, artificial pneumothorax was the method of choice, supplemented where necessary by adhesion section or in some cases by phrenic interruption. It will, therefore, not be out of place to think of collapse therapy in this series largely in terms of artificial pneumothorax. The place of this form of therapy in our armamentarium of treatment has not yet been decided, although it is as long ago as 1890 that Forlanini described his first case of artificial pneumothorax. Indeed, a study of the literature on the subject reveals that the majority of papers would suggest that the effect of artificial pneumothorax on the course of the disease is negligible or at least slight and references to the beneficial effects of this form of treatment are few. Curiously enough artificial pneumothorax is still widely practised, and, judging by current advertisements in the Medical Press, the ability to carry out such treatment is regarded as a desirable qualification in a tuberculosis medical officer. The difficulties in the way of whole-hearted commendation of this form of treatment arise, of course, firstly from lack of a control series of identical cases—if two cases of pulmonary tuberculosis can ever be identical—treated by methods other than collapse and, secondly, in the difficulty of applying statistical methods to results obtained. Indeed, one eminent tuberculosis physician put on record that in his opinion the results of artificial pneumothorax treatment were not suitable for statistical analysis.

Even in the absence of a control group, however, I make bold to claim that I have shown that artificial pneumothorax is of definite value in prolonging the life of the tuberculous patient. In a series of 1257 cases, almost one-third of them were treated by collapse therapy of which 75 per cent. was by artificial pneumothorax, and they had a probability of survival significantly greater than that for the series as a whole and one almost equal to that of those patients in the series whose disease was of such extent as to allow them to be put into stages 1 and 2 of the Turban-Gerhardt classification.

To conclude, I hope I have shown that the prognosis from pulmonary tuberculosis even in an area such as this with an incidence of and death rate from the disease well below that for Scotland as a whole is not good. Of notified patients from whom tubercle bacilli have been recovered, only 70 per cent. would be expected to be alive after one year from time of diagnosis, 44·9 per cent. would be expected to survive five years, and 29·7 per cent. would be expected to live ten years after diagnosis. Bad as the prognosis is, it is infinitely better than that experienced by patients resident in the industrial north of England.

It has also been shown that the prognosis as to life is very similar between adolescents and adults up to the age of thirty-nine years; but

adolescent males have a better prognosis than have females of the same age group. A very high percentage of these young girls were found to have advanced disease at the time of diagnosis. In the absence of any other obvious reason for this difference in extent of the disease, it is suggested that it may be due to endocrine changes in females of this age group. The prognosis for patients of forty years and over is distinctly poor. Of males, the percentages who would be expected to be alive on the first, fifth and tenth anniversaries of diagnosis are 56, 25.8 and 11.2 per cent. respectively. The corresponding percentages of females who would be expected to be alive on these three anniversaries are 45, 23.8 and 13.9 per cent. respectively. Whether these figures represent the true state of affairs in older patients or are the result of diagnosis, or at least notification being made after the disease has been active for some years, is a matter of conjecture. Whilst this may occur in a number of cases, my own view is that pulmonary tuberculosis in the older patients is a serious and fatal disease. You will have noted, too, the small number of women of forty years of age and over who contract the disease. There were 576 female patients in the whole series and only 92 were in the oldest age group. Have the majority of susceptible women broken down before forty, or is the second change in endocrine activity which occurs in women about this age a protecting or at least an inhibiting mechanism?

Those patients who were suitable for treatment by collapse methods and in whom it could be carried out—they amounted to 30 per cent. of the total—had a decidedly better prognosis than had those patients in the whole series.

Lastly, whilst those cases who were classified into stages 1 and 2 of the Turban-Gerhardt system of classification had a survival rate much above that of the whole series—92 per cent. would be expected to be alive one year after diagnosis, 72.4 per cent. would be expected to be alive five years after diagnosis and 54.8 per cent. would be expected to be alive ten years after diagnosis—those patients classed as stage 3 who could be treated by collapse methods, and they amounted to over one-third of them, had a prognosis for life substantially the same as that of those patients with less extensive disease. The proportions expected to be alive on the first, fifth and tenth anniversaries of diagnosis being 92, 65.9 and 49.5 per cent. respectively. It is on these results that I base my claim of the efficiency of collapse therapy and of artificial pneumothorax in particular in prolonging life.

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# THE CAUSES FOR THE BREAKDOWN OF DISCHARGED QUIESCENT CASES OF PULMONARY TUBERCULOSIS \*

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THE problem of the breakdown of quiescent tuberculous patients is one on which the literature is somewhat reticent. It has plenty to say about primary infection and about reinfection but very little indeed on relapses subsequent to a reinfection. Wingfield (1935), however, has given a good description of relapses in pulmonary tuberculosis.

Wingfield pointed out that a successfully treated case may live anything from five to fifty years of which only a short time will have been spent in an institution. The successful outcome may be wholly due to the treatment in the institution but in the majority of cases it is to be ascribed to efficient pre- and post-institutional handling. The handling of any case after the apparent arrest of activity is always difficult and its success depends in the main on the prevention, or early recognition and prompt treatment, of relapse.

He went on to say that relapse or reactivity, which is one of the outstanding clinical features of chronic pulmonary tuberculosis, has three forms differing completely in their characteristics. These forms are (1) New Lesion Relapse, (2) Spread Relapse, and (3) Late Relapse.

(1) *New Lesion Relapse* is due to the deposition of an entirely fresh lesion in hitherto undiseased lung. There is no known pre-disposing cause. The new lesions are usually detected as roughly circular, structureless, hazy shadows in serial X-ray films, later, they may either disappear or take on the usual appearance of the typical tuberculous lesion. The patient is often in the best physical condition when they appear and they generally occur within a period of two years. Pathologically, the new lesion in its early stages is of the nature of a simple inflammatory allergic reaction round a new deposit of tubercle bacilli; the sequel depends on the size of the infecting dose, the intensity of the allergic reaction and the immunity of the patient—either the newly-deposited tubercle bacilli will be destroyed, the allergic reaction subside and the lesion disappear to leave a minute scar or the bacilli will multiply as the allergic reaction subsides and an active spreading tuberculous lesion will result. The favourite site for these new lesions is near a pre-existing focus of disease, *i.e.* in that part of the lung which by virtue of its proximity to an existing focus possesses a higher degree of allergy than the more distant parts. The “feverish chill” or “influenzal attack” which accompanies the occurrence of a new lesion is important. X-ray examination should be made at such a time because the new lesion must be dealt with before it spreads or breaks down and if caught early these new lesions may

\* Read at a Joint Meeting of the Tuberculosis Society of Scotland and the Tuberculosis Association held in Edinburgh on 19th July 1947.

disappear surely and quickly with two months of complete rest under good conditions.

(2) *Spread Relapse* is due to direct spread of a temporarily quiescent lesion. The patient has regained his health and has no symptoms or only minimum symptoms. Radiologically the lesions have contracted, become harder in outline and shown a tendency to conversion into fibrous scars or calcified nodules. The lesions are not so soundly healed as they have appeared to be and generally within a year of return to the previous environment and habits, without at first recurrence of symptoms, serial X-ray films show that the lesions are losing their clean outline, throwing a denser shadow and slowly but definitely invading the surrounding lung tissue. The patient's environment and habits have been such as to lower physiological tone and to allow reactivation of the dormant bacilli in the lesion. This type of relapse, the "insufficient treatment" or "wrong environment" relapse is definitely indicative of a wrong mode of life for the individual concerned.

(3) *Late Relapse*, which may also be called the relapse of "late cavitation" or the relapse of middle age, results from changes in a previously "arrested" lesion without actual spread of the disease area. The lesion has remained unaltered over a long period of time and produces no symptoms; it presumably consists mainly of fibrous tissue, in the interstices of which there may be masses or nodules of encapsulated caseous material and tubercle bacilli. The sleeping lesion is disturbed by actual physical strain, by lowering of the general immunity by intercurrent disease, more commonly by direct secondary pyogenic infection and frequently by the normal lowering of general bodily vitality after middle life is passed; probably the commonest accident is for the lesion to become infected during an intercurrent pyogenic infection elsewhere in the respiratory tract. The contents of the arrested lesion become inflamed, caseation increases, the liquid material points to the nearest patent bronchiole and is evacuated leaving a cavity—or there may have been a dry, symptomless cavity for years when, either as a result of an intercurrent infection or because the patient has passed the zenith of life, insidious symptoms begin to appear. Radiologically, in serial films, changes are seen within the area of the previous shadow and they are usually indicative of cavitation—if the relapse is due to infection of a previously clean cavity, no change may be seen in the X-ray picture. Symptoms vary—there is usually an insidious general deterioration of health, loss of weight, diminution of vigour—cough and sputum appear, or, if already present, increase, there may be slight recurrent hæmoptyses, there are recurrent "colds," "influenzas," "bronchial catarrhs" or "bronchitis" unrelated to weather conditions or epidemics. There is one sure method of treatment—collapse; if that is not employed then first there must be a permanent suitable alteration of environment from the polluted atmosphere and frequent air-borne respiratory

infections of urban life to country life in a climate which suits the patient, the choice of the latter often being made only by trial and error and, secondly, there must be control, if not eradication of obvious focal sepsis in the respiratory tract.

One or two studies, notably those of Trudeau (1936) and Stephens (1941) have tended to show that various clinical features of the acute reinfection stage have a prognostic influence on the future course of the illness and on the tendency to relapse after apparent cure.

Trudeau noted that the extent of lung involvement greatly influenced the prognosis, the death rate being in direct proportion to the amount of disease ; he did not say how many of his quiescent cases survived, but of all his admissions in the period under survey, 39 per cent. of the far-advanced cases, 15 per cent. of the moderately advanced cases and only 3 per cent. of the minimal cases failed to survive five years. The prognosis in exudative disease was more unfavourable than in proliferative disease. The presence of cavities appeared to be related to a death-rate within five years which was almost twice as much as when cavities were not noted ; of cases in which the cavities increased in size during institutional treatment, 54 per cent. died within five years after dismissal, whereas if the cavities remained of the same size 34 per cent. died and if the cavities decreased, only 11 per cent. died in the same period. Again, patients whose serial X-ray examinations in sanatorium were favourable had more than twice as good a chance of being well at the end of five years from admission and only one-fourth as great a chance of being dead as those who had increased X-ray shadows in comparative films. Fever exceeding 99·6° F. on each of five successive days while in sanatorium appeared to suggest a prognosis which was equally unfavourable with that suggested by increased shadows in comparative films. Patients with both fever and an unfavourable course as shown by comparative X-ray studies had six times as unfavourable an outlook as those free of fever and with a favourable course as shown by comparative X-ray studies. Physical signs were of little value in assessing prognosis. In a follow-up of 600 admissions for three to five years, 53 per cent. had left the sanatorium in good condition and remained well, 11 per cent. had relapsed and thereafter become well again, 16 per cent. had relapsed and become chronically ill, and 14 per cent. had died ; of these groups respectively 11 per cent., 13 per cent., 29 per cent. and 49 per cent. had shown extension of disease radiologically during their stay in sanatorium.

Stephens, in reviewing 1041 sanatorium cases found that, measured by ability to work on the third, fifth and tenth anniversaries of admission to sanatorium, minimal cases had a much more favourable experience than moderately advanced cases and those in turn than far advanced cases ; thus, estimating from her published figures, for both sexes, 86·7 per cent. of cases with minimal lesions were able to work five years later as compared with 56·8 per cent. and 28·5 per cent. respectively with moderately advanced and far advanced lesions.

She noted that age on admission had no influence on the status at the specified anniversaries nor had sex, except for a slight advantage to males in the advanced stages in the first few years. Again, she analysed the records of 761 ex-patients who had resumed their work, the disease in most cases being arrested or apparently arrested, and found that patients who were originally admitted to sanatorium in the minimal stage had fewer recurrences of their tuberculosis after return to work than those admitted in the advanced stages, and that the females had fewer recurrences than the males ; in a five-year period after resumption of work about one-third of the men and one-fifth of the women who had originally been seen in the minimal stage required further treatment while the figures for those originally in the advanced stages were over one-half of the men and almost one-third of the women ; on the fifth anniversary of return to work after the first spell of treatment, 90 per cent. of the minimal cases were able to work as compared with 75 per cent. of the advanced cases.

Studies bearing particularly on environmental factors have been those of Bradbury (1933) and Keddie (1934).

Bradbury studied the causal factors in tuberculosis on Tyneside but rather with regard to association of these factors with tuberculosis in general than with recurrence of tuberculosis after quiescence. Among his conclusions, poverty is taken as being closely associated in a causal respect with tuberculosis, the principal results of poverty which lead to tuberculosis being over-crowding and under-nourishment. He submitted evidence to show that certain racial groups, notably the Irish, had a high incidence of tuberculosis, probably because of a relatively small amount of immunity to the disease. His findings also suggested that residence in tenement dwellings, presumably because of the greater overcrowding in them, was associated with a greater prevalence of tuberculosis.

Keddie investigated influences which were adverse to tuberculous patients. He concluded that delay in securing adequate initial residential treatment, whether from delay in seeking medical advice, from delay in diagnosis, or from delay in provision of treatment was a potent force in preventing ultimate permanent arrest of the lesion. Again, failure to obtain adequate institutional care, usually because of economic difficulties in the home, less often because of inadequacy of education concerning the illness, was an important adverse factor. A return from residential treatment to poor conditions of housing, to a lower standard of nutrition and to anxiety concerning the financial welfare of the family, particularly if the patient was fit for work but unemployed, was also important.

With the object of testing in the case of breakdown of quiescent cases the causative influences which have been detailed above, the writer examined the records of patients with pulmonary tuberculosis who were notified in his dispensary area in Glasgow during 1936, 1937 and 1938 and was able to find 132 patients who left hospital

with their disease in the quiescent stage. In choosing those patients, cases of pleural effusion were excluded, partly because of the good ultimate results to be expected in most cases and partly because it was often difficult in them to show that there had been a reinfection lesion in the lung itself. "Quiescent" was taken as implying good general condition without evidence of toxæmia, absence of tubercle bacilli from sputum in each of three consecutive months before discharge from the institution and evidence of retrogression of the tuberculous lesion.

Poverty as judged by an average income in the family per head per week of less than 10s., tested against survival five years after discharge appeared to be a favourable factor in quiescent tuberculosis but not significantly so. Bradbury (1933) found a marked association between poverty and the occurrence of tuberculosis. Overcrowding, as judged by an average of two or more persons per room, had no obvious relation with survival five years after discharge. It was not feasible, because of the impact of war conditions after September 1939, to test undernourishment against the same standard. It was found to be of advantage, but not significantly so, for a person to live in a main-door house (opening on to a garden or directly to the street) and if in a tenement, for him to live on the ground floor rather than at a higher level; a very small extra advantage could be detected in rehousing of tuberculous families containing quiescent cases in less overcrowded circumstances. No appreciable disadvantage was noted in the case of quiescent patients who were members of families consisting of five or more members.

Breakdowns of quiescent cases were noted as taking place uniformly through the four quarters of the year. The greatest number of breakdowns was noted in the second and fourth quarters of 1939 and the first quarter of 1940 but these were probably not to be attributed to the outbreak of war because a graph based on time of onset of breakdowns was roughly similar in shape but with a delay of eighteen months to two years to one based on time of dismissal from hospital. Quiescent cases were found to have a survival rate of 96 per cent. after one year, 82 per cent. after three years, 74 per cent. after five years, 68 per cent. after seven years and 45 per cent. after ten years; the third year after leaving hospital appeared to be that in which the greatest mortality took place. The commonest apparent causes for breakdown were overstrain or overwork, influenzal chills or colds and hæmoptysis; in this connection, it is important to note that "influenza," a "feverish chill" or a cold quite often appeared to precede a breakdown in a somewhat similar manner to the way in which a like story is often obtained at the onset of reinfection tuberculosis—much less frequently pleurisy was noted before evidence of breakdown appeared in serial X-ray films; hæmoptysis, similarly, was a first clinical evidence of breakdown. Only on one occasion did the strain of pregnancy appear to cause breakdown; the lesions in several

patients remained quiescent during and after pregnancies. By far the commonest lesion associated with breakdown appeared to be reactivation of an old lesion without extension of disease, the late relapse of Wingfield—it happened on thirty-six occasions as against six in which new lesions in previously healthy lung were found; the two in combination occurred on eight occasions. Twenty-four relapses occurred in the first year after discharge from hospital, sixteen in the second year, ten in the third year and six in the fourth year; the remaining thirteen occurred in later years.

Delay in admission to hospital had no obvious association with later breakdown of quiescent discharged cases; the most favourable results were found if there was delay of less than one month and the least favourable when there was two months' delay; delays of three months or longer were no less disadvantageous than a delay of one month. The optimum period of stay in an institution in these cases seemed to be between nine months and a year and once a case was quiescent it did not matter much whether he left with or without the consent of the medical staff.

Breakdowns were less frequent in those cases in which the original extent of the disease was minimal than in those in which the involvement of lung was moderate or extensive, and there was a smaller advantage to the moderate case as compared with the extensive case. In none was the association of extent of disease with breakdown significant. Age and sex appeared to be of no significance in determining breakdown after quiescence in the relatively small number involved in this investigation. Racial factors in so far as they could be tested had no relation to the breakdown of quiescent cases.

Too few cases have been surveyed to enable valid conclusions to be drawn as to the effect of intercurrent disease, such as diabetes mellitus or heart disease or of other infections whether of the respiratory tract or of the lung itself. Nor has it been possible to study the effects of anxiety, fatigue, lengthy travel to work and long hours of work, which are generally regarded as undesirable in quiescent tuberculosis.

The conclusion must be that largely the same factors are at work in causing the breakdown of quiescent tuberculosis as influence the occurrence of reinfection tuberculosis itself. In both instances, the organisms are able to break through the defences without obvious reason, being helped by the reduction of the resistance of the patient through adverse environmental circumstances, though not obviously by poverty or overcrowding in quiescent tuberculosis, and through intercurrent disease, usually of an infective nature.

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## PRURITUS ANI ET VULVÆ\*

By G. A. GRANT PETERKIN, *M.B.E.*, M.B., Ch.B., F.R.C.P.Ed.

PRURITUS ANI ET VULVÆ is my theme for this evening and my intention is to emphasise the importance of determining the exact factor or factors responsible for this distressing, and often refractory, complaint. Often the treatment of the condition should be undertaken by the combined operations of a gynæcologist, physician, surgeon and dermatologist. In the hope of causing controversy, I here and now assert that pruritus ani et vulvæ is more often within the province of the dermatologist than of the other specialists.

To ascertain the causes of a pruritus, a full and careful *history* must be taken—an elementary precaution that is often forgotten—as this may give the most valuable information. The patient should be asked the duration of the disease (which is important in estimating prognosis); whether any relations have been similarly affected, or have suffered from eczema, asthma or hay-fever; and whether he has had any previous skin trouble. The exact original site of itching must be ascertained, as it may have begun on the mucous membrane of the anus or vagina, or on the skin itself, while the itching may have been apparent before a rash appeared. The type of pruritus may give a clue as to etiology—*e.g.* a hot burning itching usually indicates irritation due to chemical contacts. If the pruritus occurs as sudden attacks, with an overpowering desire to scratch the part, one thinks at once of a neurodermatitis, or threadworms.

Full details of all drugs being ingested, or applied, may lead to the discovery that the symptoms are due to a purgative—*e.g.* phenolphthalein; to enemata—*e.g.* quinoxyl; or to local applications—*e.g.* nestosyl ointment, or Izal toilet paper.

A feeling of moistness or discharge from the anus, or vagina, makes one think of proctitis, yeast infection, trichomonas, and condylomata lata. Diarrhœa or constipation may account for the symptoms, and one should never forget the possibility of amœbic or bacillary dysentery, especially if the patient has been abroad.

Enquiries should be made concerning the general health, the effect of worry and hot drinks or alcohol, and whether the symptoms improved when on holiday. Needless to say, the questioning should include a careful gynæcological history, bearing in mind that pruritus vulvæ is common in post-menopausal women.

Finally, after these numerous questions one ought to have been able to assess with a certain degree of accuracy the proportion of itching due to psychological influences.

The *examination* of the patient may be divided into three main parts:—A. General. B. Local. C. Special investigations.

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A. *General*.—Particular attention should be paid to the appearance and physique of the patient—the lines of care furrowing the brow, the red-rimmed sleepless eyes, the restless limbs; the pale dry skin of the asthma-eczema subject, or the jaundiced eye and depressed air of the early hepatitis.

Skin diseases that may be of significance are thick dandruff; seborrhœic dermatitis of the folds of the skin; tinea of feet and thighs; yeast infection of the nail-folds; psoriasis; asthma-eczema, and lichen planus; while one may discover on the mucous membrane of the mouth the typical lesions of lichen planus, mucous patches, leukoplakia or buccal ulcers.

B. *Local examination* may reveal at a glance the exact cause of the itching and so indicate the correct treatment to cure the patient. Not infrequently, however, the skin appears to be perfectly normal and a considerable amount of investigation is required to discover the cause. Obviously there is no such thing as an idiopathic pruritus.

Fissures, piles and sinuses should be searched for and any evidence of proctitis or leucorrhœa noted. If the skin is damp and soggy round the anus and vulva one thinks of intestinal worms, amœbiasis, rectal carcinoma and hypertrophy of the anal glands. If there are thickened patches of skin, circumscribed neurodermatitis, lichen planus and leukoplakia are possible causes, while redness and maceration point to psoriasis, flexural seborrhœa, pyogenic infection or a fungus disease, either a true ringworm or a yeast such as *Candida albicans*.

Occasionally one discovers a warty condition on the vulva or anus—this may be due to condylomata acuminata, condylomata lata, or rarer conditions such as pemphigus vegetans, or verrucous tuberculosis. Definite ulceration may be caused by many diseases, *e.g.* tuberculosis cutis, ulcus actum vulvæ (Lipschutz), cutaneous diphtheria, tertiary syphilis, amœbiasis cutis or ordinary ecthyma.

Pediculosis pubis and scabies have been found to be the sole cause of severe itching of the genitalia and are often forgotten. If the skin is red and weeping, with an acute eczematous reaction and hot burning irritation, a contact or chemical dermatitis is probably present, and may be due to local antipruritics, especially cocaine derivatives, medicated toilet paper, or a drug taken by mouth or inserted into the rectum, vagina or urethra.

Venereal diseases should not be forgotten, as itching may be due to manifestations of syphilis, such as condylomata lata, moist papules or even primary sores; gonorrhœa, especially a proctitis; chancroid and lymphogranuloma inguinale.

C. *Special Examinations*.—Alas, we cannot all say that we always *examine the urine for sugar*—how easy it is to forget what is so obvious—but it is not so well known that a *blood sugar tolerance test* may reveal information of value. As localised itching may be the first sign of disease of the liver, especially infective hepatitis, a *van den Bergh* and *icteric index* are often worthwhile.

A *hæmatological examination* may show evidence of leukæmia or Hodgkin's disease, or an eosinophilia which might indicate many things, including intestinal worms and allergic diseases. The *stools* should be examined for threadworms, tapeworm, ascaris and *entamoeba histolytica*; if litmus paper indicates an alkaline reaction of the *fæces*, it is a sign of excessive fermentation and treatment with lactic acid milk or lactic oats, as advocated by Aitken, should be commenced.

In many cases it is desirable to take scrapings or swabs for the *microscopical and cultural examination* of ringworm or yeasts, such as *Candida albicans*, but it should be remembered that yeasts are often commensal organisms especially in women, so that their presence is not necessarily evidence that they are the cause of the pruritus. No antiseptic applications should be used for at least a week prior to examination for fungi.

Occasionally, removal of a *septic focus*, such as an abscessed tooth or a chronic appendix, has led to cure of the disease, but of course excessive zeal in the removal of possible focal sepsis is to be deprecated.

If indicated, *rectal examination*—digital, proctoscopic and sigmoidoscopic—should be performed to eliminate rectal carcinoma, enlarged prostate, amœbiasis, hæmorrhoids, etc., and of course a *gynæcological overhaul* to rule out such conditions as yeast or trichomonas, cervicitis, kraurosis and leukoplakia.

Everyone realises that *psychological factors* often play a large part in pruritus ani et vulvæ, and sometimes are even the sole cause. In patients in which these seem predominant I have found it advisable to obtain the aid of a psychiatrist, in some cases with extremely satisfactory results.

During the year 1946 I treated 107 cases, 72 of them being women, the other 35 being men with pruritus ani. I had confidently expected that the age period of most of these patients would be between 40 and 55, but was surprised to find that 19 cases were aged between 21 and 30, and 32 between 31 and 40, while only 13 and 21 were in the groups of 41 to 50 and 51 to 60 respectively.

This is explained by the high incidence of ringworm infections (22 cases) which mainly occurred in the lower age groups. Other primary causes of the pruritus were neurodermatitis, 18 cases; yeast infection, 8; asthma-eczema, 6; contact dermatitis, 6; flexural seborrhœa, 5; psoriasis, 5; staphylococcal infections, 3; condylomata acuminata, 3; psychological causes, 2; streptococcal infections, 2; cystitis, 2; carcinoma cutis, 2; enlargement of mucous or sebaceous glands, 2; kraurosis, 2; condylomata lata, lichen planus threadworms, amœbiasis, tinea versicolor, prurigo nodularis, ischiorectal abscess and tuberculous sinuses, each one.

TREATMENT—(a) *General measures*.—Lavatory paper should not be used—instead the anal region should be protected by a thick bland paste such as Lassar's before and after a motion, and nothing but cotton-wool or soft cloth used after defæcation. A sitz bath medicated

with tar or potassium permanganate will often assure the patient a good night's rest, while one can tide the patient over acute and severe attacks by hot and cold sponging, cold compresses, or heat from an infra-red lamp or even a 150-watt electric bulb. A starch poultice is one of the most soothing applications one can prescribe, and never does any harm, unlike so many antipruritics.

Cocaine derivatives are especially liable to cause a contact dermatitis; and though one may often have to prescribe an ointment containing a local anæsthetic, one should always warn the patient that it must not be used as a routine night and morning, but reserve it for use in an emergency. This drawback does not apply to the same extent to other antipruritics such as phenol, menthol, camphor and tar, and one of the most useful of prescriptions is :

R Phenol 1 dr. ; Calamin prep. 3 dr. ; Zinc Oxide ; Glycerine  
āā 2 dr. ; Milk of Magnesia to 6 oz.

But of course local applications depend to a large extent on the etiology of the disease, and the essential condition is the ability to assess what has caused the trouble. Perhaps the most useful (but colourful) antipruritic of all is Castellani's paint—(R Saturated Alcoholic solution of Basic Fuchsin, 10 c.c. ; Phenol 5 per cent. aqueous solution, 100 c.c. ; filter and add Boric Acid 1 grm. ; after 2 hours add Acetone, 5 c.c. ; after 2 more hours add Resorcin, 10 grm. Keep in a dark, well-stoppered bottle). This often gives great relief, partly because of the phenol content, and partly because a great number of these patients have a ringworm or yeast infection.

Tar is another useful drug, especially where there is no rawness ; it can be used as a paste but is often best employed as a paint—*e.g.* R Crude tar, 10 c.c. ; Benzole, 20 c.c. ; Acetone, 80 c.c. In some cases, Calomel—used either as a powder in the way recommended by Thaysen, or as a 10 per cent. paste—is helpful.

Of all the varied treatments, however, by far the most effective is X-ray therapy, though to a large extent its effectiveness depends on the cause of the disease. The rays may be used in fractional doses, *i.e.* 75 r units once weekly for four to five applications, or in single larger doses, *e.g.* 250 r or 350 r units. The great disadvantage of this treatment is that patients obtain so much relief that if they have a relapse they are apt to importune the physician for further dosage which often leads to a radio-dermatitis. This difficulty is overcome by the use of Thorium-X, a suspension of  $\alpha$ -rays in alcohol, ointment or collodion. This not only in many cases relieves the itching but even has a beneficial influence on the radio-dermatitis according to some observers.

Injections of alcohol or local anæsthetic have to be resorted to in severe cases—*e.g.* proctocaine, benacol, etc., but should be done under conditions of complete asepsis. I speak feelingly on this point, as in two patients I have been guilty of causing extremely painful abscesses.

Operations such as Ball's are frequently unsuccessful, as I have seen several patients who have stated that their itching has been even worse since their operation. A quaint treatment, introduced by Hollander, has come into vogue in the U.S.A. and seems to have given satisfactory results in many refractory cases. This is the tattooing of the itchy area with cinnabar by means of an electric tattoo machine. The bright red discolouration of the skin which results is a very definite disadvantage.

Hormonal therapy I dare not venture to more than mention before this body of experts—my impression is that even though the indication for endocrine treatment may be obvious, the results obtained are not so brilliant as one might have hoped. I trust that this remark will produce a vigorous rejoinder.

In such a chronic disease, treatments are bound to be varied and numerous—of those used with success in some cases I shall only mention auto-hæmotherapy, calcium injections, strontium bromide—orally or intravenously, and injection of spleen substance.

As the itching "doth murder sleep," a reliable sedative is often required, if only to prevent excessive scratching at night. What suits one patient does not necessarily suit another—one may find soneryl efficacious, the next luminal, and yet another chloral, but one should keep in mind two points—that opium derivatives often increase pruritus, and that phenacetin is a particularly useful drug in itchy skin conditions.

Finally, what proportion of these patients do we actually cure completely? A follow-up of cases over a ten-year period would be interesting but probably mortifying to our self-esteem! I would therefore like to make an appeal for much closer co-operation, both in hospital and private practice, between the gynæcologist and dermatologist, even by the formation of a special clinique for the investigation and treatment of the martyrs of this humiliating and demoralising scourge.

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#### DISCUSSION

*Dr T. N. Macgregor* said that, as seen in the gynæcological out-patient clinic, the vast majority of cases of pruritus vulvæ were associated with vaginal thrush or trichomonad infection. He had been disappointed to hear so little from Dr Peterkin about the management of that not inconsiderable group of cases in which no cause whatever could be elicited. He referred to the oral administration of hydrochloric acid with vitamin A concentrate, which had been of value in his hands, and asked whether Dr Peterkin had any experience of this method. He himself felt that radiotherapy in pruritus vulvæ was dangerous and should not be recommended.

*Dr Miller* said that in his experience it was unusual for patients suffering from trichomonatous vaginitis to complain of external pruritus as their

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principal symptom; a soreness rather than an itching was the more usual complaint. He was of the opinion that radiotherapy was not free from risk when employed in the treatment of irritative conditions of the vulva and before such therapy was given it was desirable, he thought, that an exact diagnosis should be made by either a gynaecologist or dermatologist. He had himself seen two cases of leucoplakia of the vulva which were being treated in this way, the presence of squamous epithelium of the vulva having been overlooked.

*Dr Clifford Kennedy* said he was sceptical of the value of hydrochloric acid and vitamin A, and, similarly, that he had been disappointed in the use of oestrogen for the post-menopausal case. X-ray therapy had yielded little success in his hands, and he had therefore resumed his former practice of injection of the affected area with proctocaine which, in many cases, gave a long period of relief.

*Dr Liston* said he thought the group of cases which the gynaecologist saw was quite different from those cases who consulted the dermatologist. Firstly, there were the pregnant women who came complaining of pruritus vulvæ due either to thrush or trichomonad infection. (He thought trichomonad cases almost always complained of pruritus.) Secondly, there were the non-pregnant, pre-menstrual women with pruritus where the bulk of cases were of trichomonas vaginalis with an associated discharge. Thirdly, there were the menopausal women with no obvious cause for the pruritus, or with pruritus associated with leukoplakia or kraurosis.

*The President* thanked *Dr Peterkin* for his address. The oral use of hydrochloric acid and vitamin A had given him very good results in the last fifteen years, in cases of severe leukoplakia in whom he had never tried the achlorhydria. For uncomplicated pruritus, however, he had never tried it.

*The President* said he congratulated *Dr Peterkin* heartily for his ability to have diagnosed the cause of the pruritus in every single one of his 107 cases.

*Dr Peterkin*, in reply, said he thought *Dr MacGregor* was probably quite right in saying that 97 per cent. of the pruritus cases a gynaecologist saw were caused by thrush or trichomonad infection.

With regard to the question of treatment with vitamins and hydrochloric acid, he had been using that treatment himself for some considerable time, but his experience was that the cases that responded to it were the asthma-eczema or neuro-dermatitis ones.

With regard to radiation therapy, *Dr Peterkin* reminded them that he did emphasise its dangers. X-ray treatment should only be used if there was a definite dermatological indication. There were certain skin diseases that did benefit, but treatment must be kept within the confines of safe dosage, and he himself never gave a dose of more than 300 r units. Treatment could alternatively be given by Thorium-X.

With regard to infections, he saw women up to the age of seventy-five with yeast infections.

Finally, *Dr Peterkin* said he would point out that he had listed three cases in which he had been able to find no cause and had referred these patients to a psychiatrist with good results. The psychiatrist had said very strongly that no amateur psychotherapy should be undertaken in such cases, as the underlying mental conflict might be severe and dangerous.

## NEW BOOKS

*A Textbook of Bacteriology and Immunology.* By J. M. DOUGHERTY, M.A., PH.D., and A. J. LAMBERTI, M.S. Pp. 360, with 102 illustrations. London: Henry Kimpton. 1946. Price 22s. 6d. net.

This book has been compiled for the benefit of the pre-medical and pre-dental student, and is of a less elaborate character than the average book on this subject in this country. It covers the usual range of medical bacteriology but in less detail than usual.

It is doubtful whether this book would be considered adequate for the medical undergraduate, but it would seem to be admirably adapted for the nurse in training.

*Bacteria in Relation to Nursing.* By C. E. DUKES, M.D., M.SC., D.P.H. Pp. viii+186, with 20 illustrations, some coloured. London: H. K. Lewis & Co. 1946. Price 12s. 6d.

This book has been prepared primarily for those who are training as Sister Tutors, but it should be equally useful to all junior nurses. Its object is to give a general understanding of bacteria, their properties and actions, without going too deeply into technical detail. There are also sections on Immunity, Sterilisation and Antiseptics and on the collection of specimens.

The book is an admirable introduction to the study of Bacteriology.

*Gynecological Endocrinology.* By P. M. F. BISHOP, D.M. Pp. viii+124. Edinburgh: E. & S. Livingstone. 1946. Price 7s. 6d. net.

This is in no sense a textbook on the subject but merely a summary of present-day knowledge aimed at helping the busy practitioner to understand the use of hormones in his work.

The author describes the endocrine control of the menstrual cycle, and the mode of action and administration of the various hormones. Precise and practical information is given for a series of common gynecological complaints. Pregnancy tests are described in some detail and there is a valuable section which includes data regarding all the commercial preparations available on the British market.

*Diseases of the Suprarenals.* By L. J. SOFFER, M.D. Pp. 304, with 42 figures. London: Henry Kimpton. 1946. Price 28s. net.

Suprarenal disorders are relatively uncommon, but the development of adrenal physiology represents one of the most dramatic and satisfactory features of modern medicine. The fuller knowledge of the chemistry of the adrenals has permitted a more thorough understanding of their diseases and has gone far towards explaining the relation of these organs to the rest of the endocrine system.

Naturally, Addison's disease claims the greatest attention in this volume, but there are also chapters on the adreno-genital syndrome and on the various tumours of the suprarenals.

Dr Soffer gives a first-class account of the present state of knowledge in this field and the book is excellently produced and well documented.

*The Medical Annual, 1946.* Edited by Sir HENRY TIDY and A. RENDLE SHORT, M.D., F.R.C.S. Pp. 426. Illustrated. Bristol: John Wright & Sons Ltd. Price 25s.

In its sixty-fourth issue this well-known Medical Annual appears once more in its limited wartime form; yet despite restricted space it offers a very comprehensive review of the advances of the past year. The capable editors have had the assistance of some forty-five eminent contributors who have well maintained the high standards of previous volumes. Wartime experiences still occupy a prominent position, but there is much information that can be of value to the civilian practitioner. This excellent publication occupies a unique position in medical literature.

*Public Health Nursing in Syphilis and Gonorrhœa.* By EVANGELINE HALL MORRIS. Pp. v+239, with 17 figures. London: W. B. Saunders Co. Ltd. 1946. Price 12s.

Miss Morris, who is an associate Professor of Nursing, begins by indicating the importance of the problem of venereal disorders and follows this with a short historical account of these diseases. The pathology, diagnosis and treatment of syphilis and gonorrhœa are described in such a way as to give the nurse a thorough understanding of the problems involved. Then follow chapters on epidemiology, clinic services and other agencies available in America. There are also important sections on Family Life Education and on the work of a Public Health Nurse.

The book is excellently produced and should service a useful purpose.

## NEW EDITIONS

*Pye's Surgical Handicraft.* Edited by HAMILTON BAILEY, F.R.C.S.ENG. Fifteenth Edition. Pp. xii+668, with 789 illustrations. Bristol: John Wright & Sons Ltd. 1947. Price 25s. net.

The new edition of this classic has been enriched by the addition of many new illustrations, and by the revisions necessary to bring each section into line with current surgical opinion. It may be confidently recommended to the house surgeon and senior student as a complete guide in which he will find the solution to all his problems.

*Recent Advances in Endocrinology.* By A. T. CAMERON, C.M.G., M.A., D.SC.EDIN. Sixth Edition. Pp. vii+443, with 74 figs. London: J. & A. Churchill. 1947. Price 21s.

Appearing first in 1933, this book has been one of the best of the Recent Advances Series. Professor Cameron gives in readily available form the latest information on various aspects of the ductless glands. He deals with biochemistry, physiology, pathology and also with the clinical states and their endocrine treatment.

Though steady progress is still being made in this subject, there is no outstanding addition in the present edition. Revision has permitted some slight improvements in the text. The chapters are well documented, so that the reader can readily find additional information on any subject in which he is specially interested.

*A Short Textbook of Midwifery.* By Y. F. GIBBERD. Fourth Edition. Pp. viii+563, with 195 illustrations. London: J. & A. Churchill Ltd. 1947. Price 21s.

To ensure that this edition is up-to-date and truly reflects the gradual changes in obstetrical thought and practice, the author has made a thorough revision of the text. Likewise new material has been added, for since the last edition penicillin has become available in civilian practice and is finding an important place in the treatment of puerperal sepsis and mastitis, while rhesus incompatibility is recognised as a cause of certain foetal and neonatal diseases as well as a factor to be considered in blood transfusions.

It is regretted that the term Albuminuria of Pregnancy has not given place to Pre-eclamptic Toxæmia. Albumen in the urine is often a late sign, and to wait for its appearance before appreciating the presence of a treacherous condition is fraught with danger. The old name carries that possibility. Again in the treatment of the condition the author advocates a total daily intake of at least five pints of fluid and lays no weight on attempting to adjust the fluid balance.

A feature of the textbook is the chapter, unavoidably rather lengthy, on Puerperal Infections. Here the dependence of the variations in the morbid anatomy and the clinical courses of these cases on the actual infecting organism is well correlated.

This edition can be confidently commended to students and practitioners as a clear and reliable statement of modern obstetrical teaching and practice.



*Glands of Destiny.* By IVO GEIKIE-COBB, M.D. Third Edition. Pp. xii+258, with 24 illustrations. London: William Heinemann Medical Books. 1947. Price 15s.

This book is divided into two parts, the first describing the various ductless glands and their functions, the second an attempt to show how these organs control the personality of the individual. Much advance in our knowledge of endocrinology has occurred in the ten years since the second edition appeared and this has necessitated extensive revision. The second part which contains a series of sketches of famous people has been less modified. Two character studies have been omitted in this edition and have been replaced by one on Edward Gibbon the historian. This thought-compelling work should be of interest to every practitioner of medicine.

*The Essentials of Materia Medica, Pharmacology and Therapeutics.* By R. H. MICKS, M.D.(DUBL.), F.R.C.P.I. Fourth Edition. Pp. x+399. London: J. & A. Churchill Ltd. 1947. Price 18s.

Advances made during the past three years have necessitated the rewriting of about a third of this book and the introduction of new sections on more recently introduced remedies. The chapters on narcotic action and anæsthesia have been remodelled using the new and accepted terminology, and the chapter on drugs used in the treatment of heart failure has been rewritten to make clearer the indications and contra-indications for digitalis and other drugs.

This is a clearly written and most readable book which can be thoroughly recommended for the use of those wishing to keep up-to-date, but, as its title indicates, it is not exhaustive, and reference must be made to larger textbooks for detailed information regarding less commonly used drugs.

*Clinical Examination of the Nervous System.* By G. H. MONRAD-KROHN, M.D., F.R.C.P. Eighth Edition. Pp. xx+380, with 126 illustrations. London: H. K. Lewis & Co. 1947. Price 16s. net.

The occupation and isolation of Norway in the recent war delayed the publication of this edition, and this has necessitated numerous alterations and additions to the text. In particular the section on angiography has been considerably enlarged and a number of illustrations added. The high standard of this work has been maintained and it can be recommended to all those interested in this subject.

## BOOKS RECEIVED

- ADLER, FRANCIS H., M.D. Gifford's Textbook of Ophthalmology. Fourth Edition. Illustrated. (W. B. Saunders Company, London) 30s.
- DORLAND, W. A. NEWMAN, A.M., M.D., F.A.C.S. The American Illustrated Medical Dictionary. Twenty-first Edition. (W. B. Saunders Company, London) 42s. Indexed 40s. Plain
- FITZWILLIAMS, DUNCAN C. L., C.M.G., M.D., CH.M., F.R.C.S. (EDIN. AND ENG.). Cancer of the Breast. (William Heinemann (Medical Books) Ltd., London) 25s. net.
- LITZENBERG, JENNINGS C., B.S.C., M.D., F.A.C.S. Synopsis of Obstetrics. Third Edition. (Henry Kimpton, London) 27s. 6d. net.
- LÜSCHER, DR ERHARD. Kurze Klinik Der Ohren-, Nasen-und Halskrankheiten. (Benno Schwabe & Co., Verlag, Basel) Gebunden Fr. 54
- MCCOMBS, ROBERT PRATT, B.S., M.D., F.A.C.P. Internal Medicine in General Practice. Second Edition. Illustrated. (W. B. Saunders Company, London) 42s.
- RUSSELL, C. SCOTT, M.A. M.B., F.R.C.S.(EDIN.), M.R.C.O.G. Obstetrics and Gynæcology. (Oxford University Press, London) 12s. 6d. net.
- WATKINS, ARTHUR G., M.D., F.R.C.P. Paediatrics for Nurses. (John Wright & Sons Ltd., Bristol) 10s. net.
- WECHSLER, ISRAEL S., M.D. A Textbook of Clinical Neurology. Sixth Edition. Illustrated. (W. B. Saunders Company, London) 42s.

# Edinburgh Medical Journal

*November-December 1947*

## NOVEMBER 1847 AND ITS SEQUEL \*

EVENTS CONNECTED WITH THE DISCOVERY OF THE ANÆSTHETIC PROPERTIES OF CHLOROFORM BY JAMES Y. SIMPSON, GEORGE S. KEITH AND J. MATTHEWS DUNCAN

By J. CHASSAR MOIR

Nuffield Professor of Obstetrics and Gynæcology, University of Oxford

### THE DISCOVERY

NOVEMBER 1847—and there was news indeed! It had been a year of wonders. Months only had elapsed since the almost incredible news had arrived that pain, even the fearsome pain of a major surgical operation, could be completely quelled. Liston himself, our own surgeon, now established in London, had used the method when amputating a leg: “this Yankee dodge beats mesmerism hollow” † had been his jubilant exclamation at the completion of that operation. And James Young Simpson, fired with enthusiasm after a visit to his one-time colleague, had daringly used the new method, not, as hitherto, for brief moments, but for extended periods of time and to relieve the pains of labour itself—nothing less!—and had found it good.

It was now common knowledge that a stupor was induced by inhaling the vapour of sulphuric ether: but word was around that something better had been found; and soon a strange name was on every lip: chloroform had arrived. Simpson again it was who, with his assistants, Duncan and Keith, had made the discovery and declared the superiority of the new drug.

And so, for decades to come, chloroform with its sweet, potent vapour was to take pride of place in almost every medical centre throughout the world—so much so, that its very name, both as noun and verb, all but ousted the learned but awkward word proposed by Oliver Wendell Holmes—“anæsthesia.”

\* A Honyman Gillespie Lecture given in the Royal Infirmary, 27th November 1947.

† A reference to the practices of Liston's much criticised colleague, John Elliotson, Professor of Medicine in University College Hospital, London, who had become a convert to the teachings of Anton Mesmer.

All that was one hundred years ago ; and in this, the centenary year, many a stirring account has been given of the introduction of anæsthesia, and not least of the part played by Simpson and his assistants in their self-imposed task of testing on themselves the effect of strange chemical vapours—experiments which we now know were far more dangerous and daring than these workers in their ardour realised—or certainly admitted.\* So, too, many a reminder has been given of that famous, late-night gathering at which the investigators, after charging their tumblers with a new substance, chloroform, and breathing the vapour, felt themselves benumbed and estranged and, after moments of drunken darkness, became aware that they were struggling on the floor amidst a tumult and turmoil of overturned tables and chairs. Professor Miller's eye-witness account of that historic event is too familiar to need repetition. So too are many of the other episodes that marked the advent of anæsthesia ; and, rather than attempt to catalogue those historic developments, I invite you to picture with me some of the men and some of the events of the Edinburgh Medical School of that day, and to sense their influence on " the shape of things to come."

### JAMES YOUNG SIMPSON

What kind of man was Simpson ? Let his contemporaries answer :—

" In his appearance Simpson was as extraordinary as he was in his social and professional relations. He was of medium stature with an enormous head, well covered with flowing locks, a light complexion, bright blue eyes, a well-shaped mouth, a short, thick neck, and broad shoulders, the whole set off by the countenance indicative of benevolence and intelligence." Elsewhere we read of " massive bent brows from under which shone eyes now piercing as it were, your inmost soul, now melting with almost feminine tenderness." A friend recalling Simpson's appearance in early years stated : " I do not distinctly recollect his personal appearance at that time, because when you set eyes on him your attention was at once completely absorbed with the genial radiance of his whole expression, and when he tossed back his long black hair with his hand you saw a strong perpendicular cliff of a forehead, and beneath it benevolent, bright, clear eyes, indicating a man of genius and kind sympathy. This young man was James Simpson. Young though I was then, I was irresistibly attracted to him." The then Duke of Argyll recorded : " I do not know that I ever met any man in whom genius was written more visibly in his face, voice and manner." Yet another writer, after referring to Simpson's arresting appearance and peculiarly winning smile, continues : " He had a prodigious and very accurate memory ; and

\* In a later experiment Simpson was discovered by his butler lying apparently lifeless on the floor : he remained unconscious for two hours. On another occasion when visiting the Professor of Chemistry, Sir Lyon Playfair, he was with difficulty dissuaded from trying on himself a new chemical substance just come to hand ; instead, two rabbits were submitted to test : some hours later these animals were found dead in their cage.

as he possessed an unusual facility in extracting information out of all who had it to give, it may be understood that his stores of knowledge were by no means the result of drudgery. . . . Many are the anecdotes afloat as to the scrapes he got into by the forgetful neglect of his patients, and of how easily his beguiling manner usually succeeded in helping him out of them. Always overwhelmed with work of very various kinds, and being of most unmethodical habits, it happened not infrequently that important engagements were wholly forgotten."

Simpson's father was a baker in the village of Bathgate. His mother, a woman of Huguenot descent, was an active and kindly creature who, at the time of James's birth, took over the family business—then at a very low ebb—and managed it with decidedly more success than did her husband. James, the seventh child of a family of eight, was soon marked as a lad of unusual intelligence. As was so often the custom in Scots families, the other members—in this case particularly an elder brother, Alexander—stinted themselves in order to provide funds to enable the chosen boy, then thirteen years of age, to enter the University.

In Edinburgh, James boarded in Adam Street along with two medical students—Macarthur, one-time junior master at the Bathgate School, and John Reid, a previous schoolmate (who in later years was to become Professor of Physiology at St Andrews University). Macarthur seems to have exercised some disciplinary influence on the younger boys, urging them to strenuous work and himself setting the pace by cultivating the habit of doing with as little as four hours of sleep a day. James at first attended the Greek and Philosophy classes of the University but before long his companions' talk, their enthusiasm for their medical studies and particularly their devotion to the anatomy lecturer—the incomparable but ill-fated Robert Knox, round whom in recent years more than one stage-play has been written—enticed him from the "Humanities" to the dissecting rooms.

A side-light on the conditions of university students of the time is afforded by the following items of expense. Rent of a room cost Simpson 3s. a week. The cost of postage on letters was, however, relatively high, and at 6½d. per package the lad and his family did not feel justified in exchanging more than one letter each way during the whole of his first term from home. In Simpson's note-book the following items are strangely linked together: "Finnen Hadies 2d. and Bones of the Leg £1, 1s."; "Subject £2,\* Spoon 6d. and Bread and Tart, 1s. 8d."; "Snuff 1½d. and *Early Rising* 9½d."

Simpson attended his new classes with diligence but not, it appears, with any outstanding success. Least of all did he excel in midwifery (a subject not then generally incorporated in the medical curriculum), for this was the one lecture in which he regularly fell asleep. When,

\* The relatively high cost of anatomical material is a reminder that this was the time of the "Resurrectionists," and of the notorious Burke and Hare murders, when high prices were demanded for corpses supplied to medical schools.

however, we recall that Simpson was cultivating the habit of doing with less and less sleep and studying from the very early hours of the morning; we may feel sympathy with him when late afternoon arrived and Hamilton, the Professor of Midwifery, was timed to start his lectures.

In those days a thesis written in Latin—the language in which all final medical examinations were then conducted—had to be presented before Graduation. Simpson's thesis on peritonitis won particular attention and gained for him an Assistantship with the Professor of Pathology. In this post he seems to have acquitted himself well. A few years later, following the "earnest suggestion and advice" of his chief, he turned his attention to midwifery. This he did with a zeal and vigour that were now becoming his outstanding attributes; and when in course of time Hamilton retired, Simpson, then twenty-eight years of age, made a bid for the vacant Chair.

The election developed into a fierce battle. At that time the appointment was in the hands of the Town Council, and the selection of a candidate depended on many issues besides that of mere professional competence. It is astounding to learn that this contest with its canvassing, pamphleteering, public lectures, and the cataloguing and publicising of his personal museum cost Simpson the sum of no less than £300! Amidst the public excitement aroused by the election we find a human touch. It had been represented to Simpson that one of his opponents, being a married man, had some advantage for this particular Chair. A few days later Simpson disappeared, to return from Liverpool married, and on an equal footing with his rival! It is only fair to add, however, that the lady of his choice was no stranger; and we are permitted to suppose that the reason for her suitor's sudden surge of ardour was fully revealed—and fully condoned! Let me now read the letter sent a few days later by Simpson to this lady's father.

"I was this day elected *Professor*. My opponent had 16 and I had 17 votes. All the *political* influence by both the leading Whigs and Tories here was employed against me; but never mind—I have got the chair in despite of them, Professors and all . . . Jessie's honeymoon and mine is to *commence* tomorrow."—Your affectionate son, J. Y. Simpson.  
*Tuesday, 4th Feb., 1 Dean Terrace.*"

This was success indeed for a young and comparatively unknown man; but in the sudden flood of fortune a cross-current had already appeared. He had offended, and fallen foul of, the great James Syme—the "Napoleon of Surgery" as he has been called—then at the height of his power. Far-reaching consequences were to follow.

### THE EDINBURGH FEUDS

Feud and controversy were the order of the day. While the Edinburgh medical life was possibly enlivened, it was most certainly

embittered by the professional jealousies and disputes on every hand. Colleagues who did not agree expressed their opinions of each other in the bluntest terms; and documents containing scathing indictment or damning innuendo—each man to his taste—were printed in a surprisingly unexpurgated form in the public press of the time. True, neither Simpson nor Syme indulged openly in such conduct, but a belief was current that Syme was concerned with certain anonymous letters written with intent to damage Simpson's reputation.

In later years, when, after much study and thought, Simpson proposed a means of arresting hæmorrhage from amputation stumps involving the use of steel pins—acupressure, it was called—Syme became incensed at the intrusion into his field of work. He had Simpson's pamphlet brought on a tray into his operating theatre, and there, after scornfully reading the title to the assembled students, and denouncing it as "vulgar insolence," he rent the offending document to shreds and threw the remains into the tub of sawdust kept in those days for receiving dismembered limbs. Next day, Simpson's lecture theatre was crowded to the door. In due course the Janitor appeared, bearing a tray, and on it Syme's own textbook of surgery. Simpson followed. Excitement was unconfined. With a disarming smile, Simpson opened the book at a marked page, read the words: "torn vessels never bleed; *torsion does no harm*"; and gently closing the volume he continued with the lecture of the day. This episode, childish and trivial though it may be, reflects the animosities of the time, and incidentally reveals Syme's weakness: his petulance and self-sufficiency. Had it been otherwise, it is probable that the surgery of the day would have been even further enriched—for it certainly lacked nothing in the ability of its exponents.

In time, the feud spread to the younger members on both sides. Thus, in later years, we find Simpson opposed to Lister (Syme's one-time assistant and son-in-law, now Professor of Surgery in Glasgow) and repudiating his new doctrine of antisepsis. This opposition became bitter and vehement in the case of Lawson Tait (Simpson's protégé) and resulted in Tait's evolving methods which he misleadingly represented as being opposed to Listerism and proving the fallacy of that doctrine. This was the beginning of the fight between antiseptic and aseptic systems—as foolish a squabble as has ever marred medical progress, for the one is clearly evolved from the other, and both owe origin to the fundamental teaching so carefully propounded by Lister in his early papers. In other words, the use of carbolic acid, which has often been ignorantly regarded as the embodiment of Listerism, was quite clearly stated by Lister himself to be a means to an end, and not necessarily the method that would finally prevail for the sterilising of infected surfaces or body cavities. Nevertheless, under Tait's forceful and, one fears, unscrupulous methods of publicity, immeasurable damage was done to Listerism; and that great doctrine unquestionably faltered in its spread to the southern parts of this land.

## THE BACKGROUND

In these times, when anæsthesia is accepted as a matter of course, how many of us give thought to the surgery of a hundred years ago? Can we picture the scenes of those days? And do we realise the magnitude of the operations then undertaken? Liston, Syme and Fergusson, to name but three surgeons of the time, performed feats of surgery that even to-day would daunt any but the stoutest heart. The Fergusson "lion" forceps is a familiar object in the operating theatre, but how many realise that this fierce instrument with its powerful teeth and vice-like grip was designed for the removal of the jaw-bone itself, and that Fergusson successfully performed this operation twenty years before anæsthesia was thought of! Lawson Tait, in a letter regarding Listerian methods—to which he was opposed—writes:—

"Does Lord Lister remember, as I do, the awful inguinal aneurism, in which the patient was slit, as it seemed, from the middle of the thigh up to the umbilicus, the gluteal aneurisms, the removal of the lower jaw, the fearful œsophagotomies, and, most of all, the thirty-seven consecutive cases of ligature of the femoral artery for popliteal aneurism, *not one of which died!*"

It would be easy—for there is vast material to choose from—to recount the hideous suffering endured in those seemingly far-off days. I ask your indulgence for only two extracts, both greatly shortened, from accounts of true episodes. The first is from a letter addressed to Simpson, and written by a doctor who had himself submitted to a major operation.

"Suffering so great as I underwent cannot be expressed in words, and thus fortunately cannot be recalled. The particular pangs are now forgotten; but the black whirlwind of emotion, the horror of great darkness and the sense of desertion by God and man, bordering close upon despair, which swept through my mind and overwhelmed my heart, I can never forget, however gladly I would do so . . . I watched all that the surgeons did with a fascinated intensity. I still recall with unwelcome vividness the spreading out of the instruments; the twisting of the tourniquet; the first incision; the fingering of the sawed bone; the sponge pressed on the flap; the tying of the blood vessels; the stitching of the skin; and the bloody dismembered limb lying on the floor.

Before the days of anæsthetics, a patient preparing for an operation was like a condemned criminal preparing for execution. He counted the days till the appointed day came. He listened for the echo on the street of the surgeon's carriage. He watched for his pull at the doorbell; for his foot on the stair; for his step in the room; for the production of his dreaded instruments; for his few grave words, and his last preparations before beginning. And then he surrendered his liberty, and revolting at the necessity, submitted to be held or bound, and helplessly gave himself up to the cruel knife."

The other is from that gem of medical reminiscence, *Rab and His Friends*, by Dr John Brown. It refers to an operation undertaken

by James Syme in the Minto House Hospital on Ailie, the wife of James, a carter, who had her breast removed for a malignant tumour.

"Next day, my master, the surgeon, examined Ailie. There was no doubt it must kill her, and soon. It could be removed—it might never return—it would give her speedy relief—she should have it done. She curtsied, looking at James, and said, 'When?' 'Tomorrow,' said the kind surgeon, a man of few words. She and James and Rab and I retired. I noticed that he and she spoke little, but seemed to anticipate everything in each other. The following day, at noon, the students came in, hurrying up the great stair. At the first landing-place, on a small well-known blackboard, was a bit of paper fastened by wafers, and many remains of old wafers beside it. On the paper were the words, 'An operation to-day. J.B., Clerk.'

Up ran the youths, eager to secure good places: in they crowded, full of interest and talk. 'What's the case?' 'Which side is it?'

Don't think them heartless; they are neither better nor worse than you or I: they get over their professional horrors, and into their proper work; and in them pity—as an *emotion*, ending in itself or at best in tears and a long-drawn breath lessens, while pity as a *motive*, is quickened, and gains power and purpose. It is well for poor human nature that it is so.

The operating theatre is crowded; much talk and fun, and all the cordiality and stir of youth. The surgeon with his staff of assistants is there. In comes Ailie: one look at her quiets and abates the eager students. That beautiful old woman is too much for them; they sit down, and are dumb, and gaze at her. These rough boys feel the power of her presence. She walks in quickly, but without haste; dressed in her mutch, her neckerchief, her white dimity shortgown, her black bombazeen petticoat, showing her white worsted stockings and her carpet-shoes. . . .

Ailie stepped up on a seat, and laid herself on the table, as her friend the surgeon told her; arranged herself, gave a rapid look at James, shut her eyes, rested herself on me, and took my hand. The operation was at once begun; it was necessarily slow; and chloroform—one of God's best gifts to his suffering children—was then unknown. The surgeon did his work. The pale face showed its pain, but was still and silent. . . .

It is over: she is dressed, steps gently and decently down from the table, looks for James; then, turning to the surgeon and the students, she curtsies—and in a low, clear voice, begs their pardon if she has behaved ill. The students—all of us—wept like children; the surgeon hopped her up carefully—and, resting on James and me, Ailie went to her room, Rab following."

## THE SEQUEL

So much for the background; the sequel is scarcely less astonishing. Such is the perversity of human reasoning that no sooner had the pain-destroying properties of ether and chloroform been proved than there was an outcry, and a denunciation of their use. Anæsthesia was unnecessary; it was unnatural; it would undoubtedly increase the mortality of operations. Regarding its use in childbirth, it was "an unnecessary interference with the providentially arranged process of healthy labour"; it might induce convulsions; it might cause an infant born under its influence to develop into an idiot; it abolished



"a desirable, salutary, and conservative manifestation of life-force" \*; it was "a decoy of Satan apparently offering itself to bless women, but in the end hardening society, and robbing God of the deep earnest cries which arise in time of trouble, for help." In short, it transgressed scriptural teaching: *in sorrow thou shalt bring forth children*.

Simpson's fighting qualities were now roused. By every means in his power he waged battle for the recognition and acceptance of anæsthesia. In his own very wide practice he used it extensively and he exhorted others to do likewise. His great abilities as lecturer and writer were pressed to service: lectures were delivered, pamphlets distributed, endless letters written to prove that a new era in surgery had begun. His methods were various. To his medical colleagues he relied on carefully presented facts and figures. Thus, he collected evidence from many hospitals to show that the mortality from amputations was less, and not more, when these operations were performed under anæsthesia. As was his wont, he headed this paper with quotations from Shakespeare:—

"Why dost thou whet thy knife so earnestly?"

. . . "Shylock must be merciful"

"On what compulsion must I? Tell me that!"

To a lady recently arrived from Ireland, who had complained that the method was "unnatural" Simpson is said to have replied, "How unnatural it is for you, Madam, to have swam over from Ireland to Scotland against tide and wind in a steamboat!" To the religious bigot † with his quotations from Genesis, he replied that the evidence was in favour of anæsthesia, and poked fun at him by recalling that on the occasion of the first recorded operation—the removal of a rib—the Lord God had caused a deep sleep to fall on Adam. But his chief concern was the distress of earnest-minded people with deep-seated convictions and honest qualms regarding the morality of the method. This he met by contending that a study of the Hebrew roots shows that the word used in the disputed passage, and translated in our Bibles as "sorrow," does not mean suffering in the sense of pain, but is better rendered as labour, toil, or physical exertion. More particularly, his answer to these thinking people was epitomised in the two New Testament quotations that headed his paper in reply to the religious critics—one from Timothy (I, iv, 4): "For every creature of God is good, and nothing to be refused if it be received with thanksgiving"; and from James (iv, 17): "Therefore to him that knoweth to do good and doeth it not, to him it is sin."

\* Meigs, Professor of Midwifery in Boston, so described the pains of labour. Elsewhere he speaks of anæsthesia as "unnecessary as shown by the birth of past myriads."

† Dr Chalmers, the great Scottish divine, was not opposed to anæsthesia; he referred to the critics as "small theologians." The loudest and most persistent objectors were, in fact, members of Simpson's own profession.



SIR J. Y. SIMPSON



BUST OF JAMES MATTHEWS DUNCAN  
PRESERVED IN THE ABERDEEN MEDICAL SCHOOL  
*Photograph kindly supplied by Professor Lockhart*



SIR ALEXANDER R. SIMPSON

*(From Comrie's "History of Scottish Medicine,"  
by permission of the Wellcome Foundation Ltd.)*



CARICATURE IN CLAY OF  
SIR ALEXANDER R. SIMPSON



MAIN STREET, BATHGATE

In the house on the left Simpson was born on 7th June 1811.

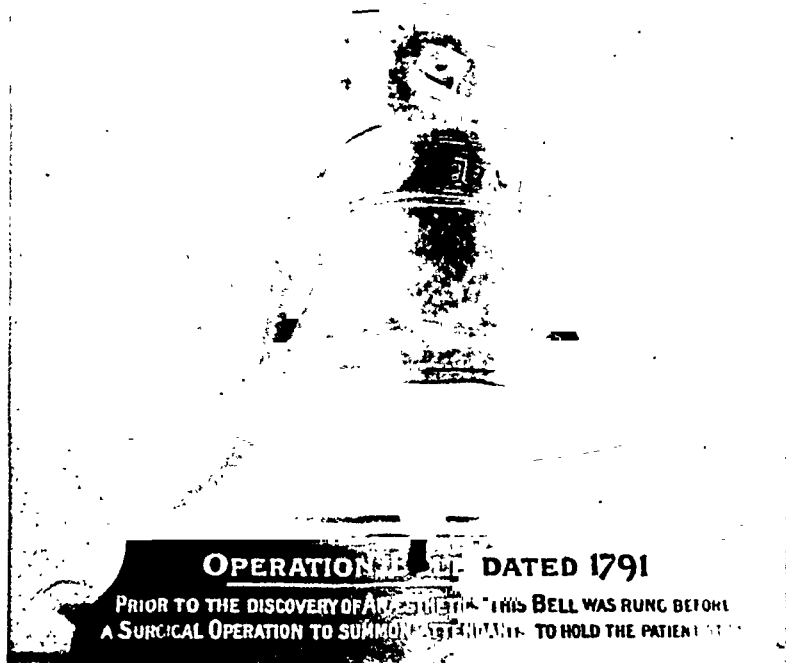


THE DINING-ROOM OF FIFTY-TWO QUEEN STREET IN WHICH THE  
ANÆSTHETIC PROPERTIES OF CHLOROFORM WERE DISCOVERED



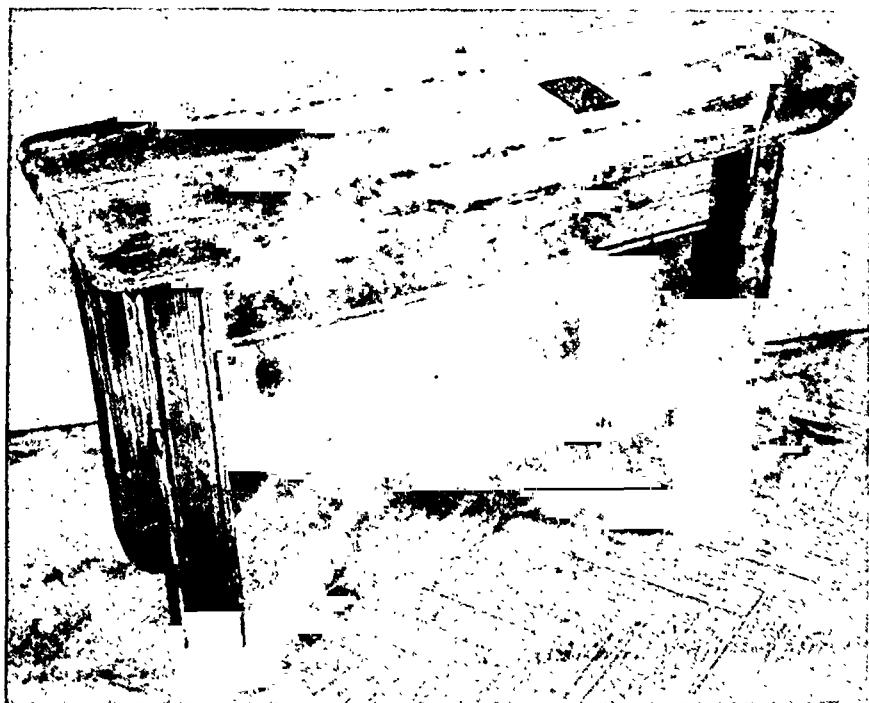
NO. 52 QUEEN STREET, EDINBURGH

Between the windows of the centre house there is now the inscription "Sir James Young Simpson lived in this house from 1845 to 1870, and in 1847 discovered the anæsthetic powers of chloroform."



A BELL USED IN PRE-ANÆSTHETIC DAYS TO SUMMON ATTENDANTS TO THE  
OPERATING ROOM TO HOLD THE PATIENT STILL

*From the London Hospital*

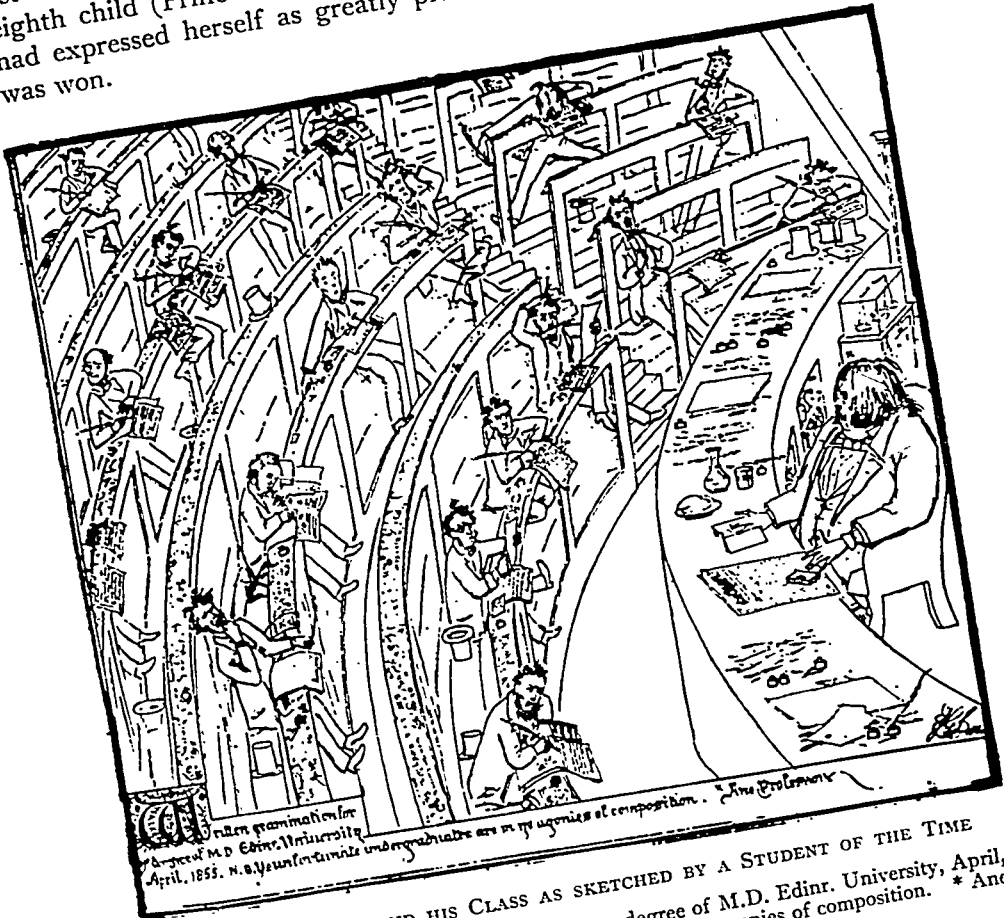


THE TABLE IN UNIVERSITY COLLEGE HOSPITAL, LONDON, ON WHICH LISTON  
PERFORMED THE FIRST OPERATION UNDER ETHER ANÆSTHESIA IN BRITAIN,  
21ST DECEMBER 1846.

The holes on the sides are for accommodation of the straps by which (in pre-anæsthetic days)  
the patient was bound down and immobilised.

# NOVEMBER 1847 AND ITS SEQUEL

For several years opinions swayed—at least so far as the application of anæsthesia to midwifery was concerned; then news came to an astonished world that Queen Victoria herself, for the birth of her eighth child (Prince Leopold) had had chloroform administered and had expressed herself as greatly pleased with the result. The battle was won.



SIR J. Y. SIMPSON AND HIS CLASS AS SKETCHED BY A STUDENT OF THE TIME  
The caption reads: "Written examination for ye degree of M.D. Edinr. University, April, 1855. N.B. Ye unfortunate undergraduates are in ye agonies of composition. \* Ane Professor."

## SIMPSON'S ACHIEVEMENTS

Simpson's name is so closely linked with the story of chloroform that the other achievements of that great man are sometimes forgotten.

He was a prodigious worker. His day started in the early hours, often as soon as 4 a.m. when he rose to deal with correspondence and to prepare his lecture for the students.

His practice ranged over the whole of the country—England as well as Scotland—and often his only sleep was that snatched in the cold, primitive railway carriages of the time.

A glimpse of his mode of life is given in an account by Spencer Wells of a visit to Simpson on New Year's Night 1855.\*

"The night was spent with Simpson, Priestly, and others, in visiting the prison, whiskey shops, and low haunts of that city†; next day among Simpson's private and hospital work. At night Simpson entered into a learned discussion at the Royal Society on some of the Buddhist opinions and monuments of Asia compared with the symbols of the ancient sculptured 'standing stones' of Scotland. After the meeting, Simpson drove him (Spencer Wells) to a country house, the scene of the ball in *Waverley*, where patients were visited in the middle of the night; the house and grounds seen by moonlight, and Edinburgh only reached in the early morning. That day, Mr Wells did his operation in the Edinburgh Infirmary, and returned to London in the evening, Simpson having been in bed only two hours all this time—no uncommon example it was said of his marvellous activity and power of work."

Simpson's speed of work was likewise amazing. This is illustrated by the manner of introduction of chloroform anæsthesia. The famous "party" took place on 4th November; five days later Simpson used chloroform in a midwifery case, and the following day read a paper at an Edinburgh Medical Society on the nature and properties of the drug, and giving details of its use in operations conducted by his colleague Professor Miller. By the 15th November (eleven days after the discovery) Simpson was able to record its administration on no less than 50 occasions.

His contributions to medical science, particularly his own specialty, were so extensive that long before the publicity of anæsthesia arrived he had already achieved a world-wide reputation and had been appointed Physician to the Queen for Scotland.‡ By introducing the uterine sound and the compressed sponge tent for dilating the cervix uteri, he was able to explore the interior of the uterus and thus to make the diagnosis of many abnormalities of that organ a matter of scientific certainty rather than of clinical speculation. Freeland Barbour described Simpson's contributions thus: "Gynæcology stood like a rich harvest to be reaped, but the instruments had not been provided. Simpson brought these, and such store of corn fell to his scythe that those who followed appeared only as reapers."

\* *Brit. Med. Journ.*, 1870, 2, 52.

† A reference to Simpson's frequent practice of escorting parties of "New Town" citizens through the slums of the "Old Town" in order to arouse their interest in philanthropic work.

‡ By strange chance, a letter notifying him of this honour arrived while he was conducting his first anæsthetic delivery (version and extraction of an 8 lbs. fœtus in a woman with contracted pelvis, the conjugate diameter of which was judged to measure no more than  $2\frac{1}{2}$  inches). In a letter to his brother, dated 22nd January 1847, Simpson wrote: "Flattery from the Queen is perhaps *not* common flattery, but I am far less interested in it than in having delivered a woman this week *without* any pain while inhaling sulphuric ether. I can think of nought else."

Simpson's wide reputation \* may be judged by the following incident. On the occasion of a visit to Paris, Simpson was received in Madame Victor Hugo's salon. "The excitement," it is recorded, "was something tremendous, and for a time you could hear the sound ss-ss-ss running through the room as there passed from mouth to mouth the exclamation, 'C'est Simpson, C'est Simpson!'"

In his later years, Simpson entered into another strenuous battle, this time on the question of "Hospitalism," proving beyond doubt that a terrible hazard was added to surgical operations when these were performed within the walls of our old institutions. To avoid this evil he urged the construction of small, airy, easily movable wards—and, be it remembered, he made this plea years before Lister had laid bare the secret of sepsis. Another remarkable example of Simpson's foresight is shown in the following words contained in a graduation address given half a century before the date of Röntgen's great discovery:—

"Possibly even by the concentration of electrical or other lights we may render many parts of the body, if not the whole body, sufficiently diaphanous for the inspection of the practiced eye of the physician or surgeon."

Simpson's interests ranged over the whole field of medicine, yet he found time to make a deep study of antiquarian lore, in which, indeed, he became a leading authority. He himself investigated no less than 160 leper houses in Scotland, and his monograph on this subject, containing 500 references to ancient documents, is said to be the most authoritative in existence.

This extraordinary man's career can be epitomised by the following contrasts.

Simpson's professional fitness for the Chair of Midwifery had been doubted. Before a dozen years had elapsed his was the best known name in the whole medical world.

His ability to attract patients and to hold the interest of medical visitors had been questioned. In later years his house was insufficiently large to receive those who sought his presence. No scientist, traveller, historian, politician or writer considered his visit to Scotland complete until he had had conversation with James Young Simpson. Fifty-two Queen Street, became the centre of attraction; and it was quite customary for a dozen or more guests to be present for breakfast or lunch—each of whom contributed all that was best in conversation, stimulated by the skilful leading of his genial host.

\* "Sir Byrom Bramwell in an address to the Royal Medical Society said of him: 'Simpson was, in my opinion, the greatest, by far the greatest, of my teachers.' This tribute gains in significance when in another part of the same address he says: 'I speak advisedly when I say that, so far as my knowledge enables me to judge, there never was any medical school in the world at any period of its existence which, at any one time, had such a number of extraordinarily able and distinguished men as had the Medical School of Edinburgh when I became a medical student in 1865.'" (Miller, D., *Trans. Edin. Obst. Soc.* (1936-7), Session xcvi, 1.)



In Bathgate, "the urchins of the neighbourhood," we are told, "used to amuse themselves by distracting the baker's lad at his Latin." Half a century later this lad was to become a Freeman of the City of Edinburgh, an Honorary Member of almost every medical society in the world, the recipient of innumerable honours, including degrees from Oxford, Dublin and other universities, the Order of St Olaf from the King of Sweden, and, from our own Queen, a Baronetcy—the first ever to be given to a doctor or university professor in Scotland.

When he arrived in Edinburgh he was, by his own statement, "very, very young; very solitary, very poor and almost friendless." At his death, it is scarcely an exaggeration to say that the world mourned. Tribute was paid in Parliament by the Prime Minister, Mr Gladstone. In Edinburgh, as the hour of his funeral drew near, all business in the City ceased. The University closed its classrooms, the Stock Exchange suspended transactions, the traffic was stilled and an assembly estimated to number 30,000 people watched the mourners, stretched in procession the entire length of Princes Street, accompany the bier to Warriston where, according to his wish, Simpson was buried. A proposal to secure his burial in Westminster Abbey was declined by the family.

Great man as he was, and despite all the honour thrust upon him, Simpson had many critics. As Clark has quaintly put it, "Simpson was somewhat economical in his recognition of help received from others." This refers to the fact that Waldie, a Liverpool chemist, had proposed the use of chloroform to Simpson, and had indeed given him a fair indication of the effect to expect, but had not received more than brief public acknowledgment; also, that Matthews Duncan had, we now know, tried the effect of chloroform on himself prior to the famous evening "party." It has also been alleged—but with scant justification—that Simpson did little, until a very late date, to counteract the belief that soon spread amongst the common people that he, Simpson, was the introducer of anæsthesia—an honour that quite clearly belonged to his American contemporaries.\* It is not surprising therefore that Simpson with his love of controversy had detractors, and even enemies, as well as friends. Here let me quote from an obituary notice:—

"We shall attempt no judgment or criticism on local or personal feuds, but shall merely remark that there is clearly something real in the influence of the northern air, and remind our readers that it was a Scotch dog of whom it is mentioned that he was moody and unhappy because 'he could not get enough o' fechtin'.' That Sir James was not more to blame than others we believe highly probable; to prove that he was no less so we are forced to leave to those who are better acquainted with the facts."

In view of these remarks it is right to add that there is abundant evidence that Simpson never bore a personal grudge against critics,

\* See Storer, H. R., *Edin. Med. Journ.* (1911), 7, 12.

but, on the contrary, was ever eager to repair a strained or broken friendship.

Another notice in the journals about this time may interest you.

"At a meeting of a committee, presided over by the Earl of Dalhousie, the form of a national memorial to the late Sir J. Y. Simpson was agreed upon as follows. First, a monument and a statue in Edinburgh; second, a marble bust in Westminster Abbey; third, a hospital in Edinburgh for the diseases of women, constructed on those principles which Sir James so often and so clearly expressed; fourth, similar hospitals in London and Dublin should sufficient funds be obtained."

### THE CO-DISCOVERERS

So much has the story of chloroform been dominated by the name of Simpson that little notice has been taken of the co-discoverers of the effects of the drug. These men were George Skene Keith, Thomas Keith and J. Matthews Duncan.

George Keith was born at St Cyrus, Kincardineshire, where his father was parish minister. After education at Aberdeen and Edinburgh he travelled extensively in the Near East and on his return became assistant to Simpson. It was at this time that he took part in the chloroform experiments: he was the first person ever to be rendered fully unconscious by the drug. In a letter written in 1891 to Simpson's daughter, Keith states: "... I began to inhale it a few minutes before the others. On seeing the effects on me, and hearing my approval before I went quite over, they both took a dose, and I believe we were all more or less under the table together, much to the alarm of your mother who was present." Miss Simpson elsewhere states: "My aunt often spoke of Dr Keith's ghastly expression when, ceasing to kick, he raised his head to the level of the table and stared with unconscious eyes on them."

In later years Keith developed one of the largest medical practices in Edinburgh, but appears to have become more interested in diet and general hygiene than obstetrics. His book, *The Fads of an Old Physician*, was received with some interest, but more amusement: and it was to Keith both a disappointment and grim satisfaction that his critics, one by one, died before him leaving him behind, a living but lonely proof, he believed, of the truth of his theories. He lived until 1910 reaching a grand age of ninety-one.

Thomas Keith, George's younger brother, is also said to have taken part in anæsthesia experiments and was probably a spectator on the occasion of the famous "party." He was an apprentice to Simpson—one of the last doctors in Scotland to receive a clinical training by that time-honoured system. After graduation, and an assistantship with Syme, he interested himself in surgery and later became a pioneer ovariologist.

The early history of this operation is a story in itself—one of

intense interest to gynæcologists, for it was the experience gained in the removal of ovarian cysts that prepared the way for all later abdominal surgery. Keith's results were outstandingly good—probably the best of the time—and far surpassed those of his friend, the famous Spencer Wells, whose mortality rate over a large series of cases averaged more than 50 per cent. Keith's success can be attributed to his particular method of dealing with the ovarian pedicle, involving the extensive use of cautery, and the fact that most of his work was done in a private house apart from the general surgery of a hospital with its attendant sepsis.

In later years, Keith migrated to London to join his previous colleagues and friends, Matthews Duncan and Joseph Lister. There, with his son Skene, he continued his work on ovariectomy.

James Matthews Duncan was a graduate of Aberdeen University and one-time assistant to Simpson. He became famous for his very remarkable investigations on a great variety of gynæcological and obstetric problems. He, together with the American gynæcologist, J. Marion Sims, laid the foundation of our knowledge concerning the problems of fecundity and sterility. The publication of his researches on this and many other subjects caused a considerable stir and deeply influenced subsequent teaching.

As a clinician and teacher, Matthews Duncan had few equals, but his conservative tendencies restrained him from venturing far into the then rapidly opening field of surgery—a shortcoming which, incidentally, brought down on him the contempt and wrath of his more enterprising contemporary, and one-time colleague, Lawson Tait.

On Simpson's death, Matthews Duncan was the natural successor to the Edinburgh Chair of Midwifery, but the Selection Committee, still dominated by the Town Council, passed over his claim in favour of that of Alexander R. Simpson, Sir James's nephew. Generous by nature and reticent in talk, Matthews Duncan gave no indication of his bitter disappointment at this decision, but a few years later when the post of Lecturer and Physician Accoucheur to St Bartholomew's Hospital in London was offered to him he immediately accepted.\*

In London, Matthews Duncan took fresh root and thoroughly identified himself with the practice and traditions of his new hospital. He completely reorganised the teaching of his specialty and made that department the most outstanding of its kind in London—a reputation that to this day is jealously guarded. His private practice developed almost embarrassingly and included, before long, members of the Royal Family. His scientific achievements were honoured by

\* St Bartholomew's Hospital appears to have been well disposed to obstetricians from the North, for during most of the fifty years prior to Matthew Duncan's appointment, the post had been held by Scottish Graduates (J. T. Conquest, Edward Rigby, and Robert Greenhalgh). Incidentally, it had once been offered to Sir J. Y. Simpson but had been declined. ("History of St Bartholomew's Hospital," Norman Moore, *St Bartholomew's Hospital Reports*, 1890.)

his election to the Fellowship of the Royal Society; and his integrity and wisdom received highest recognition by his crown appointment as Member for England in the recently formed General Medical Council.

Matthews Duncan seldom referred to the part he played in the chloroform discovery, presumably because he preferred to avoid a controversial subject and one that might have embittered his relations with, and later, the memory of, his one-time chief.

### SIMPSON'S SUCCESSION

Now to turn to one last topic. As just stated, the vacant Chair of Midwifery passed to Sir J. Y. Simpson's nephew (son of the brother who had so greatly helped him in boyhood days). There is no doubt that the almost mystical reverence and awe in which the name of Simpson was held by them was the reason for this choice, for Matthews Duncan was generally considered to be the man on whom Sir J. Y. Simpson's mantle should by right have descended. The medical journals of the time bluntly expressed this opinion prior to the election; the following is a sample of their comment subsequent to the event:—

“Dr Matthews Duncan, whose claims were considered by every member of the profession in this country who knew anything of the matter as well as the leading obstetricians abroad, to be unmistakably superior to those of other candidates, had been passed over, and a gentleman who, as far as we have been able to learn, possessed no special claims at all to the appointment, has been elected . . . when we come to ask why their selection fell upon Dr Simpson, we confess we are utterly unable to answer the question unless it be that the successful candidate is a relation of the late Professor. . . . Throughout the whole kingdom, we may say, there is a universal feeling of disgust and indignation at the election and of sympathy with Dr Duncan. . . . The students of the University have even thought fit, in large numbers, to request Dr Simpson to resign the Chair to which he has been appointed.”

At a meeting of Edinburgh Graduates held in London, a speaker used the following words (again published with relish, and, we may suspect, some vindictiveness, by the editors of the day):—

“No event which has recently occurred at the University of Edinburgh has caused so much indignation and astonishment as the election . . . with regard to Dr Simpson I have nothing to say except that whatever eminence he may yet achieve, he occupies, at present, in the minds of those who knew medical literature, a very inferior position . . . although he may have given occasional lectures for his uncle he has never given a course of lectures on midwifery or any other subject.”

Another speaker who ventured the opinion that there had been a slight excess in the disparagement of Dr Alexander Simpson was answered, we are told, with shouts of “No, no!”

Alexander Simpson was far from being the nonentity his critics

supposed ; on the contrary, he did much to enhance the reputation of the school, and he well justified the faith shown in him by the selection committee.

With those events preceding it, there is little wonder that the inaugural lecture of Alexander Simpson was of an unusual nature, as the following report will show :—

“ Half-an-hour before the time, numbers of elderly citizens, including a few clergymen, began to arrive and ultimately formed a considerable portion of the audience. By 2 o'clock every corner of the immense classroom was densely packed, the doors and passages being entirely blocked up. Shortly afterwards the Principal, preceded by the Mace-bearer, followed by Professor Simpson and other members, entered by a side door. . . . The demeanour of the students plainly indicated a stormy meeting. Dr Simpson's self-possession seemed never to be disturbed from first to last. His reception on rising cannot be described otherwise than as equivocal. His friends applauded lustily. After waiting a few minutes, amidst a perfect babel of noises, he was allowed to proceed. He began by referring to the appointment of the previous incumbent of the Chair thirty years previously when he was interrupted by another burst of noise. The uproar seemed to be directed against the unctuous and somewhat funereal tone of voice which appeared to be natural to the speaker. . . . He thereupon began at once to explain the recent origin of the now prevalent views as to menstruation. As he proceeded, isolated phrases such as ‘ menstrual flow ’ and ‘ menstrual period,’ and other technicalities which were almost alone audible, seemed, from a variety of causes, to fall incongruously on the ears of his audience and were received with shouts of laughter and uproar. . . . The din again grew fast and furious, and was increased by one of the ringleaders shouting through a grating in the roof. He, however, was caught, and taken into custody. . . . At this time Professor Christison rose and was greeted with loud applause. One voice with a well-marked highland accent enquired, ‘ Who are you ? ’ to which the Professor replied that he had joined the University in 1811 and he surely did not require to explain who he was at this time of day. Since his first connection with the University, said Dr Christison, he had never seen so uproarious an assemblage of students ; whereat several voices replied something about there never having been so great provocation. ‘ Why should not every man have a fair hearing ? ’ enquired the Professor energetically, and this sentiment, in the abstract, was cheered to the echo.

On Dr Simpson resuming, however, the interruptions continued more or less. At one point the whole audience rose to their feet to observe an altercation between two students in the centre of the crowd ; and these two individuals engrossed the attention of everyone from the Principal downwards for a space of several minutes. The cry of ‘ The Town Council ’ was raised now and again, some members of that body being understood to be present. Other sources of confusion were introduced and Professor Simpson concluded his lecture short of the end. . . . Meanwhile, several extemporary orators among the crowd mounted to their desks and communicated their views concerning the personages and the events of the day.”

Was ever a professorship less auspiciously launched ! It is pleasant indeed to record that A. R. Simpson rose superior to all his critics

and proved a worthy successor to his great uncle. With him history reaches almost to the present day, for many in this room will remember the gentle mannered, good humoured, pious gentleman—and recall too, his absent-mindedness and his surprising but lovable lapses that were so eagerly seized on by the students of the day and elaborated into tales now immortalised in college lore.

### A BACKWARD GLANCE

A full century has run its course. How do we now view the affairs of 1847? Some may question whether the discovery of the properties of chloroform—"delicious and dangerous"—coming at a time before the use and scope of the safer ether anæsthesia had been fully determined, did not do more harm than good. Be that as it may, the indirect effects were so profound and far-reaching that subsequent medical history would have been very different but for the events of that extraordinary time. By the discovery and, still more, by the tremendous battle waged by Simpson against prejudice, indifference and bigotry, the general adoption of anæsthesia was immensely hastened, and the scope of surgery and of midwifery immeasurably increased. As for the Edinburgh Medical School, it already stood in high esteem; but still greater was its name to become and still more was it to attract the highest talent from distant lands and cities by reason of the arrival, years before, of that boy from Bathgate—"very, very young; very solitary. . . ."

I have spoken of great times and great men. A precious heritage has been passed on to us. Solemn thoughts are stirred as we think back over the century: and when next we see the surgeon at work let us spare a thought, I beg, for the Ailie of a hundred years ago and the many, many like her, and, with Simpson, rejoice in the chosen words by which, in slightly adapted form, he heralded his announcement of the use of anæsthesia in childbirth:—

"Not poppy, nor mandragora  
Nor all the drowsy syrups of the world  
Shall ever medicine thee to such sweet sleep. . . ."

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## THE CORPUS LUTEUM HORMONE \*

By G. F. MARRIAN, D.Sc., F.R.S.

THIS lecture will be largely concerned with certain aspects of the biochemistry of the corpus luteum, and in particular with the use and misuse of certain chemical methods which have been widely used in recent years for assessing the endocrine activity of the latter.

I must begin by reviewing very briefly a few of the main facts about the physiology of the corpus luteum. The principal functions of the corpus luteum hormone are: (i) to prepare the uterus for the implantation of the fertilised ovum, and (ii) to maintain the pregnancy should fertilisation and implantation of the ovum occur. The characteristic progestational changes which the hormone produces in the uterine endometrium give us the name by which the hormone is now known—*progesterone*. The progestational changes in the uterine endometrium are actually not produced by progesterone alone, but by progesterone acting synergistically with the oestrogenic hormone.

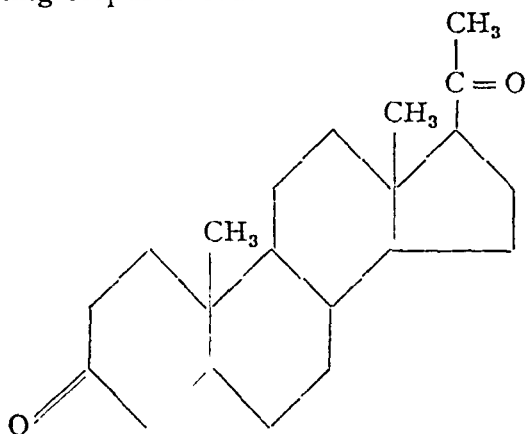
In the menstrual cycle the sequence of events in which these two hormones are involved is as follows: After the degenerative breakdown of the endometrium at menstruation, the latter becomes regenerated under the influence of oestrogenic hormone secreted by the growing follicle. This phase of the cycle, the "follicular phase," lasts about nine to ten days and is characterised histologically by a thickening of the endometrium and a lengthening of the endometrial glands. Ovulation usually occurs at about the fourteenth day of the cycle and is followed by formation of the corpus luteum and secretion of progesterone. The latter acting synergistically with oestrogen leads to the branching of the previously tubular endometrial glands which is characteristic of the progestational endometrium. This "luteal phase" of the cycle lasts to about the twenty-sixth or twenty-seventh day, when the corpus luteum degenerates and the secretion of progesterone decreases. Immediately afterwards menstruation begins.

If fertilisation and implantation occur the corpus luteum does not regress but is maintained in a state of functional activity and increasing amounts of progesterone and of oestrogen are secreted. There is a considerable weight of evidence which indicates that from about the twelfth week of pregnancy onwards the production of progesterone and oestrogen is largely, if not completely, taken over from the ovary by the placenta. This evidence may be briefly summarised as follows:—(i) Both oestrogen and progesterone are present in the human placenta; (ii) many cases have been recorded of pregnant women going to full term without mishap after bilateral ovariectomy; (iii) such pregnant ovariectomised women continue to excrete in the urine considerable amounts of oestrogenic hormone and of a certain metabolic product of progesterone. It is of interest that

\* A Honyman Gillespie Lecture delivered in the Royal Infirmary, Edinburgh, on 6th November 1947.



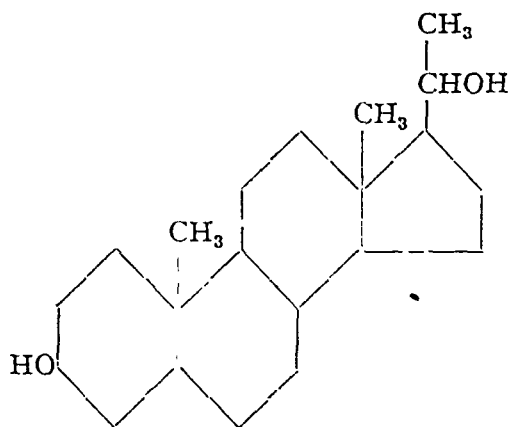
it is at about the twelfth week of pregnancy, when the change-over in hormone production from the ovary to the placenta is believed to take place, that abortion is most likely to occur. It seems probable that abortions at about this time may sometimes be due to a failure of the placenta to supplement adequately the failing endocrine activity of the degenerating corpus luteum.



I. Progesterone

Let me turn now to more chemical topics.

Progesterone was isolated as a chemically pure substance in 1934 by four different groups of workers almost simultaneously—Butenandt, Westphal and Hohlweg,<sup>1</sup> Slotta, Ruschig and Fels,<sup>2</sup> Allen and Wintersteiner,<sup>3</sup> and Hartmann and Wettstein.<sup>4</sup> Very shortly after-



II. Pregnane-3 ( $\alpha$ ), 20 $\alpha$ -diol  
 Allopregnane-3 ( $\alpha$ ), 20 $\alpha$ -diol  
 Allopregnane-3 ( $\beta$ ), 20 $\alpha$ -diol

wards the structure of the hormone (I) was completely elucidated by Butenandt and co-workers<sup>5</sup> and Fernholz.<sup>6</sup>

Much of our recent knowledge concerning the rôle of progesterone in the human reproductive cycles has been obtained by studying the excretion of one of its metabolic products which is found in urine. This metabolic product, known as *pregnenediol*, was isolated from human pregnancy urine,<sup>7</sup> and its structure (II) elucidated<sup>8</sup> several

years before progesterone was isolated. Its metabolic relationship to the latter was therefore unsuspected at that time. As soon as the structure of progesterone had been determined the possibility was clearly envisaged that pregnanediol might be formed in the body from the hormone by the reduction of the two ketonic groups and the double bond.

Proof of the metabolic relationship between the two compounds followed within a few years. In 1936 Venning and Browne<sup>9</sup> isolated from human pregnancy urine as its sodium salt a complex of pregnanediol and glucuronic acid, and Venning<sup>10</sup> subsequently devised a method by which this sodium pregnanediol glucuronide (NaPG) could be determined gravimetrically in a roughly quantitative manner in human urine. The discovery of NaPG and the development of a method for its determination in urine were events of supreme importance. Together they form perhaps the greatest single contribution that has ever been made to our knowledge of the physiology and biochemistry of the corpus luteum.

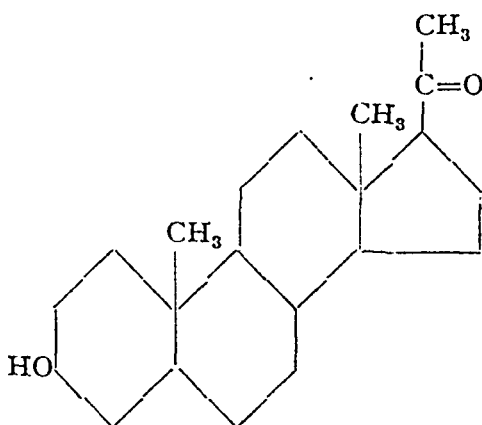
Using this method of determination Venning and Browne were able to trace a convincing parallelism between the excretion of NaPG and the production of endogenous progesterone during the menstrual cycle and during pregnancy. In the menstrual cycle they found<sup>11</sup> that NaPG was excreted only during the luteal phase, whilst during pregnancy<sup>10,11</sup> they observed that it was excreted in increasing amounts up to term and that the excretion then fell precipitously. Finally, they showed<sup>11</sup> that the administration of progesterone to women "in whom there was a reasonable certainty that no corpus luteum was present" was followed by the appearance of NaPG in the urine. Thus the status of pregnanediol as a product of the metabolism of progesterone was proved beyond any reasonable possibility of doubt.

Pregnanediol, or more correctly pregnane-3 ( $\alpha$ ), 20 $\alpha$ -diol, is not the only metabolic reduction product of progesterone which is present in human urine. Two stereoisomers of pregnanediol (II) and three stereoisomeric partial reduction products of progesterone which are saturated hydroxy ketones (III) have also been detected. The amount of these other metabolic reduction products of pregnanediol in urine are probably, however, considerably less than the amount of pregnanediol.

The question of where in the body progesterone becomes reduced to pregnanediol is one of considerable interest. At one time it was thought that the conversion might take place in the uterine endometrium itself, and thus the interesting possibility was raised that the reduction of progesterone to pregnanediol might be intimately associated with the physiological effects produced by the former. The evidence favouring this belief was as follows:—Venning and Browne<sup>12</sup> were unable to isolate NaPG from the urine of a hysterectomised woman after the administration of progesterone, while Hamblen, Ashley and

Baptist<sup>14</sup> observed that curettage during the luteal phase of the menstrual cycle was followed by an abrupt fall in NaPG excretion. On the other hand Buxton and Westphal<sup>15</sup> showed that NaPG appears in the urine of men after the injection of progesterone, so that it is clear that even though the reduction of progesterone to pregnanediol may occur in the endometrium it certainly can be effected elsewhere in the body also.

The excretion of pregnanediol during the menstrual cycle and during pregnancy must now be considered in rather more detail. The original experiments of Venning and Browne<sup>11</sup> indicated that pregnanediol first appears in the urine in detectable amounts about twenty-four to forty-eight hours after ovulation, the probable time of ovulation having been fixed in a number of cases by the occurrence of intermenstrual pain. These experiments also showed that the



III. Pregnan-3 (α)-ol-20-one  
Allopregnan-3 (α)-ol-20-one  
Allopregnan-3 (β)-ol-20-one

pregnanediol excretion then rises to a variable maximum of about 2-8 mg. per twenty-four hours about halfway through the luteal phase of the cycle and finally falls abruptly about one day before the onset of menstruation. Venning and Browne observed very large variations, however, in both the amount and duration of pregnanediol excretion in different individuals. The original findings of Venning and Browne have been amply confirmed by a number of workers, including Hamblen, Ashley and Baptist,<sup>14</sup> Wilson, Randall and Osterberg<sup>16</sup> and Cope.<sup>17</sup>

The excretion of pregnanediol during pregnancy has been studied by Browne, Henry and Venning,<sup>12</sup> Venning,<sup>10</sup> Smith and Smith,<sup>18</sup> Bachman, Leekley and Hirschmann,<sup>19</sup> and many others. Up to about the tenth week of pregnancy the average daily excretion of pregnanediol is about 10 mg. From about the tenth week onwards the amount excreted rapidly increases and reaches an average maximum of about 75 mg. per twenty-four hours at approximately the thirty-eighth week. From then until term the amount of pregnanediol excreted decreases slightly and immediately after parturition falls

precipitously. It must be emphasised that all workers have found that the values obtained from normal cases at the same stage of pregnancy show a very wide scatter. Thus Bachman *et al.*<sup>19</sup> have recorded values at the twentieth week varying between about 18 and 40 mg. per twenty-four hours and between about 60 and 150 mg. at the thirty-seventh week.

At this point I must digress to discuss briefly but critically a few of the methods which have been used for the quantitative determination of urinary pregnanediol.

Venning's method, which until recently was used almost exclusively by all workers in the field, appears to give reasonably accurate and reproducible results when more than about 15 mg. of pregnanediol per twenty-four hours is present in the urine. With urines containing smaller concentrations of pregnanediol, however, the method is somewhat unreliable. Because of this, most of the figures reported in the literature for pregnanediol excretion during the menstrual cycle and in early pregnancy should, in my opinion, be regarded with some suspicion. Various other methods of determining pregnanediol have been suggested, and some of these are superior in many respects to the original Venning procedure. Astwood and Jones<sup>20</sup> in 1941 developed a method by which free pregnanediol is determined gravimetrically after hydrolysis of the NaPG in the urine by acid. Talbot *et al.*<sup>21</sup> subsequently greatly increased the sensitivity of this method by estimating the pregnanediol colorimetrically instead of gravimetrically. This "Astwood-Talbot" method is of interest since it is the prototype from which two useful procedures of some clinical value have been developed recently. One of these is the well-known pregnancy diagnosis method of Guterman.<sup>22</sup> This is merely a simplified and shortened version of the Astwood-Talbot method by the use of which very roughly quantitative determinations of pregnanediol can be completed within a few hours. The other method developed from the Astwood-Talbot procedure is one which Drs Gough and Sommerville have worked out in my department.<sup>23</sup> They have elaborated rather than simplified the Astwood-Talbot method and have in consequence developed a procedure which is somewhat more sensitive and accurate than any others that have so far been described. By this method they can determine with satisfactory accuracy as little as 0.4 mg. of pregnanediol in one-fifth of a twenty-four-hour specimen of urine. It should be particularly useful for the study of pregnanediol excretion in non-pregnant women.

We must next consider what conclusions concerning endogenous progesterone production we are entitled to draw from urinary pregnanediol determinations. We must enquire in the first place whether the urinary pregnanediol represents the greater part of the endogenous progesterone production or whether it represents only a small proportion thereof. The only available evidence bearing on this problem has been obtained from experiments in which urinary

pregnanediol has been determined after the administration to women of known amounts of progesterone.<sup>11, 13, 17, 24</sup> The figures for the efficiency of conversion of exogenous progesterone into pregnanediol obtained by such experiments are not at all consistent with one another, varying as they do from about 8 to 45 per cent., and it is clear that further work needs to be done on this very important problem. It is, however, abundantly clear from these results that we are not justified in assuming yet that there is any quantitative relationship between urinary pregnanediol and endogenous progesterone production—a conclusion arrived at by Cope<sup>17</sup> some years ago. It is worth while stressing this point since it has been all too frequently assumed in the past that the urinary pregnanediol is a reasonably exact measure of the endogenous progesterone output.

We must go on to enquire whether urinary pregnanediol has any qualitative significance in regard to endogenous progesterone production. Strictly speaking the answer should be that it has not. Thus we know from the work of Cuyler, Ashley and Hamblen<sup>25</sup> and of Horwitt, Dorfman, Shipley and Fish<sup>26</sup> that desoxycorticosterone administered to human subjects gives rise to pregnanediol in the urine. It is not known whether desoxycorticosterone is produced in the human adrenal gland, but it is at least possible that it is, and we are therefore not justified in concluding that the presence of pregnanediol in the urine necessarily means that progesterone is being formed in the body.

The depressing conclusion is forced upon us, therefore, that urinary pregnanediol determinations give us no reliable information at all concerning endogenous progesterone production. In fact the position is not as bad as this. Although pregnanediol determinations can give us no absolutely reliable information about progesterone production, they can give us a great deal of information which has a fair probability of being correct and which has considerable clinical value. Let us see what this information is.

Pregnanediol determinations may be of value for the diagnosis of anovulatory menstrual cycles, provided that one is using a method sufficiently sensitive to detect with certainty as little as 1-2 mg. in a twenty-four-hour sample of urine.

Pregnanediol determinations are of value for the early diagnosis of pregnancy. The work of Wilson and Randall,<sup>27</sup> Hain and Robertson<sup>28</sup> and of Buxton<sup>29</sup> in the years 1939-40 indicated that the presence of pregnanediol in the urine at or above the normal level found in the luteal phase of the menstrual cycle after a missed period should provide an early indication of pregnancy. This suggestion has recently been taken up by Guterman<sup>22</sup> and using the modified Astwood-Talbot method of determining pregnanediol, which has already been mentioned, he has shown that pregnancy can be rapidly diagnosed with an accuracy as satisfactory as that given by the Friedman method. This method of pregnancy diagnosis

has been used by others in the United States<sup>30, 31, 32</sup> and to some extent also in this country. Although Guterman's original claims for its reliability seem to have been rather over-optimistic, it seems likely that the method has come to stay as a useful routine laboratory method.

In pregnancy pregnanediol determinations would seem to have some value for the diagnosis of imminent abortion or of foetal death. In early pregnancy a complete absence of pregnanediol from the urine or a low and progressively falling pregnanediol excretion is indicative of an imminent abortion (*cf.* Cope,<sup>33</sup> Guterman<sup>34</sup>). The same findings in late pregnancy may indicate foetal death. Low pregnanediol excretions have been reported by many workers in pregnancy toxæmias and in pregnancy complicated by diabetes. Low pregnanediol figures are not invariably seen in these conditions, however.

The physiological and biochemical relationships between progesterone and the oestrogenic hormone are of considerable academic interest and practical importance. There is some evidence that the oestrogenic hormone not only acts synergistically with progesterone in producing the progestational changes in the uterine endometrium, but is concerned also with the reduction of progesterone to pregnanediol and with the production of the former from the corpus luteum and placenta.

It has been mentioned that there is some rather inconclusive evidence that the uterine endometrium is the principal site of reduction of progesterone to pregnanediol in women. If this evidence be accepted the claims made by Venning and Browne<sup>13</sup> and by Smith and Smith<sup>35</sup> that pre-treatment with oestrogen or the simultaneous administration of oestrogen increases the excretion of pregnanediol from administered progesterone would seem to be reasonable. It can well be imagined that whereas an atrophic endometrium might be too metabolically inert to effect the reduction of progesterone, an endometrium stimulated by oestrogen could do so. On the other hand, Cope<sup>17</sup> could find no evidence to indicate that oestrogen increases the formation of pregnanediol from progesterone. It would be fair, therefore, to state that at the present time there is no conclusive evidence to indicate whether or not oestrogen does facilitate the reduction of progesterone to pregnanediol.

The work of Westman and Jacobson<sup>36</sup> and of Robson<sup>37</sup> indicates that oestrogens have a direct effect, not mediated by the pituitary, on the maintenance of the physiological activity of the corpus luteum. According to the work of Smith and Smith,<sup>38</sup> however, the production of progesterone is stimulated by certain uncharacterised oestrogen metabolic products rather than by the oestrogens themselves. This work led the Smiths recently to suggest that incipient progesterone deficiency in pregnancy might be forestalled by administering sufficient oestrogen to provide increased amounts of these oestrogen metabolic products. Following up their own suggestion they investigated the

effect of stilbœstrol administration upon the pregnanediol excretion of a pregnant diabetic woman who had a previous history of pre-eclampsia.<sup>39</sup> The results of this experiment seemed to show quite clearly that pregnanediol excretion may be stimulated by stilbœstrol and the Smiths therefore concluded that the latter is effective in increasing the production of progesterone from the placenta. Accordingly they have recommended that stilbœstrol administration should be used "as a preventive measure to be tried in cases with a history of repeated accidents in pregnancy which may be referable to progesterone deficiency, namely, abortion, premature delivery, pre-eclampsia, eclampsia, or intra-uterine death." This recommendation has aroused considerable interest amongst clinicians, and at various centres has been acted upon.

I am not qualified to discuss whether the various pregnancy mishaps listed by the Smiths are indeed wholly or partially caused by a deficiency of progesterone, and I do not propose to attempt to do so. I must, however, emphasise two somewhat relevant points which I think should be noted by the clinicians. Firstly, as we have already seen, there is little justification for assuming that an increased pregnanediol excretion necessarily is the result of an increased progesterone production. Secondly, evidence is already accumulating to show that stilbœstrol administration during pregnancy does not invariably result in an increased pregnanediol excretion.<sup>24, 40</sup>

To conclude let me summarise as follows. Largely as a result of the pioneer work of Venning and Browne a great deal has been learned during the past ten years about the biochemistry of the corpus luteum hormone and in particular about the clinical significance of variations in urinary pregnanediol. In fact we now know enough to realise how much more we have to learn. Such progress as has been made in this field has resulted from a collaboration between the clinician and the biochemist. The unsolved problems which are of interest to the clinician and the biochemist alike can, and I have no doubt will be solved by a continuation of this collaboration.

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# SKELETAL TRACTION AND ANTERIOR DE-COMPRESSION IN THE MANAGEMENT OF POTT'S PARAPLEGIA\*

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THOUGH it is my duty and pleasure to make this report, please bear in mind that the achievements to be recorded are the works of my colleague, Mr Alexander, who has done many of the operations; of the resident medical staff; and especially of the nursing staff whose part is so arduous; and of the tuberculosis experts who have so kindly helped us with advice and encouragement, taught us to make shells, shared the care of patients with us—I am thinking especially of Professor Cameron and his successor at East Fortune—Dr Murray.

This is an *interim* report—it concerns procedures for Pott's paraplegia which we started only three years ago. You may expect the final report in 1964.

Under the guidance of tuberculosis experts we consider our spinal problem in a rather single-minded way—or should I say double-minded—as professional guardians of the spinal cord—and as amateur orthopædists. We think a patient with permanent paraplegia might be better dead—and indeed most of them do die from its complications. No risk of this terrible calamity should be incurred if it can be avoided by timely treatment. We also aim at as straight and stable a vertebral column as possible.

PREVIOUS TREATMENTS.—Pott's disease exhibiting early paraparesis is traditionally treated by fixation in corrected or partially corrected position in recumbency, and in a high proportion of cases the paraparesis soon recovers. No other local treatment except later bone grafting in most cases is required. In this connection we believe that skeletal traction can be a valuable adjunct in correcting posture and in securing adequate fixation—especially in upper dorsal and cervical disease.

For paraparesis which fails to respond to such treatment, laminectomy, the laminotomy of Sir John Fraser, and abscess evacuation by costo-transversectomy have been extensively tried. Each has been highly successful in a moderate proportion of cases, but each has failed in a somewhat high proportion. Our recent experience suggests that success attends these measures only when they are successful in evacuating directly or indirectly a sufficiently fluid intraspinal abscess which has been acting as a major factor in compressing the cord. Our experience further indicates that solid structures which require direct exposure for their removal are much more frequent causes of cord

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compression. In these circumstances the operations mentioned cannot but fail. Laminectomy carries the additional objection of removing one of the few healthy stabilising supports of the diseased vertebral column and of compromising the effectiveness of later bone grafting operations. The compressing agency is always anterior to the theca—hence the need for a direct exposure of this area. Carrying this principle into effect we have achieved a high proportion of success in cases where the former operations had failed and in fresh cases. Mr Norman Capener of Exeter has independently developed and carried out operative treatment on similar lines and I believe with similar results.

### CLINICAL MATERIAL

The series in which we have used skeletal traction and anterior decompression for Pott's Paraplegia consists of 21 patients, 6 in 1944, 9 in 1945, 4 in 1946, and 2 so far in 1947.

Plaster shells, with *skeletal traction* only, were used in 3 cases. Skeletal traction was applied also in 5 of the operated cases. It will be more extensively used by us, with or without operation, in future. *Anterior decompression* was carried out in 18 cases.

The average age in the series is 29; the youngest patient was 4; the oldest 65; there were 6 children under 12 years of age.

The *vertebral levels* affected were: 1 atlanto-axoid; 3 cervico-dorsal; 4 upper dorsal; 6 mid-dorsal; 6 lower dorsal; 1 dorso-lumbar.

The average *duration of vertebral disease* from first known symptoms was about 2 years, excepting 3 cases in which disease had been evident for 12, 13 and 26 years.

The average *duration of recognisable cord compression* was mostly 1-2 years—the shortest duration was 5 weeks and the longest was 9 years.

The *paraplegia* at the time of our special treatment was graded as:—total in 4 cases; severe or subtotal in 7 cases; moderate (unable to walk) in 8 cases; slight (just able to walk) in 2 cases. In 2 cases upper as well as lower limbs were involved. In 6 cases spontaneous spasms were very severe; they were present to a lesser degree in most of the cases.

*Spinal fluid block* was complete in 15 cases, and partial in 4. In 2 unascertained.

The *vertebral deformity* was graded as:—extreme 4, severe 4, moderate 10, slight 3. The diseased bone was decalcified and eroded in 16; sclerosed in 5. Perivertebral abscess shadows were evident in all but one case. The cause of compression—a rather large sequestrum—was detectable by X-ray in only one case.

In the 18 operated cases the *cord compressing agent* was:—displaced, persisting disc in 8; dense bone of "internal gibbus" in 4; sequestrum in 3; solid debris in 2; fluid abscess in 1.

*Previous Treatment.*—Prior to anterior decompressive operation or skeletal traction treatment, 17 of the series of 21 had been immobilised in recumbency with varying efficiency and for variable periods. Most of them, at least latterly, had been efficiently postured and immobilised. A few had had halter extension applied. Three had had ineffective costo-transversectomy operations and each had a discharging sinus in consequence. One had had an ineffective laminectomy; one an ineffective bone graft; and one an ineffective lateral decompression (at our own hands).

*General health* at time of special treatment. Only one of our patients, so far as ascertained, had active tuberculous disease elsewhere—a woman of 45 years with early miliary spread involving the kidneys especially—she died of uræmia. About two-thirds of the patients showed signs of severe tuberculo-toxæmia. This was often aggravated by toxæmia associated with urinary infection, with bed-sores, with constipation and other effects of visceral dysfunction. In 6 cases these adverse factors were greatly aggravated by severe spontaneous and reflex spasms of paralysed limbs and trunk—interfering with sleep, causing pain, aggravating vertebral disease by strong, uncontrollable movements, and aggravating bedsores by traumatic friction. This is a veritable vicious circle,—for as the paralysis increases so do the uncontrollable spasms, which, in turn, aggravate the vertebral disease and the paralysis. It is one of the several indications for urgent, effective release of the spinal cord compression. In about one-third of the patients the general health was fair to good—the more chronic cases who had had well-organised sanatorium care.

**SKELETAL TRACTION.**—Orthopædists have recognised for many years that powerful traction could be applied without discomfort, provided the pull was applied directly on bone. Many years ago this principle was applied in fractures of the cervical portion of the vertebral column by attaching “ice-tongs” to the skull. The appliances have been perfected and that which we now use is one designed by Blackburn. It is essential that it should be of rustless steel. For treatment of tuberculous spines we have further improved the traction arrangements by building a metal rod—like the bowsprit of a ship—as an integral part of the plaster shell. The fixation is still further improved by adjusting a straight wooden edging to the rim of the head piece, upon which the projecting cross-member of the “tongs” rests. For the face-down position this is especially important for the whole weight of the head can be taken on the “tongs” and the face can be left entirely free and open below. Mobile foot supports are arranged as an integral part of the plaster shell.

For cervical and upper dorsal disease a moderate foot-down tilt of the shell provides sufficient counter-traction by body weight—5 to 10 lbs. pull is easily maintained in this way. For mid or lower dorsal disease, if stronger traction is desired, the tibiæ can be attached by transfixion pins and stirrups to fixed foot pieces of the shell, and a

strong spring attached to the skull traction tongs. We have used up to 20 and 30 lbs. pull in this way, and have so reduced the thoracic deformity and projecting sternum in 2 cases that the alternative use of an anterior shell became possible.

The chief advantages of the method are that the patients are more comfortable in dorsal and especially in ventral shells. The degree of fixation is far superior to any other available method—bone fixed to plaster. The deformity is much more efficiently corrected and maintained in correction. One of our patients—an obese young woman with cervico-dorsal disease had the tongs continuously in place for  $10\frac{1}{2}$  months; another, atlanto-axoid disease, for 5 months; many for 3 or 4 months.

One little girl had continuous treatment on angled Whitman frame and halter traction for 18 months, and again for 9 months after a few months' interval. Her paraparesis had been advancing in spite of this for 2 years and had reached almost complete paralysis. Within a week of application of effective shell and skull traction there was marked improvement. Skull traction was continued for  $3\frac{1}{2}$  months and cord recovery was then almost complete. Afterwards that position was maintained in a simple shell. At the end of a year spinal cord functions were normal.

The case of a young women provides an example of the use of traction in atlanto-axoid disease. She had experienced pain in the arms for 2 years, stiff neck 1 year, tetra-paresis—Brown-Sequard pattern—for 10 weeks, due to pressure of displaced odontoid process on medulla. In addition to luxation, due to joint disease, there was small secondary erosion at base of the odontoid. The luxation was reduced by skeletal traction; and a bone graft was then inserted. The tetraplegia had vanished 7 days after traction was started in 1944. The patient in 1947 is now heavily engaged in badminton and golf for one of the northern counties.

I would not yet care to suggest criteria of indications for traction, but I think that in very many cases of Pott's disease, with or even without paraplegia, better results, with less discomfort may be secured by its use.

**ANTERIOR SPINAL DECOMPRESSION OPERATION.**—As already remarked, there are weighty reasons for exposing the "internal gibbus" and decompressing the anterior surface of the theca there. The principal reasons are that the compressing agent is always anterior and in most cases it is solid and must be directly exposed and removed.

The more prominent the gibbus, the easier is a lateral approach to it. The skin incision curves widely to one or other side of the external gibbus. Superficial muscles are cut near the spine and the erector spinæ is displaced inwards to give an imbricated closure; we have had only two cases of post-operative sinus formation. The posterior ends of several ribs are removed, with corresponding

transverse processes and the corresponding pedicles and adjacent portions of vertebral bodies are removed. This gives access to the "internal gibbus" and the compressing agent can be removed. The anterior surface of the theca is fully exposed, and as the compressing agent is removed, fluid pulsation can be seen to return to the theca. In most of our cases, the disease was in its destructive, erosive phase and these procedures were easy. In 5 cases the disease was partially healed. Dense sclerosed bone was encountered and was difficult to remove without risk of damage to the compressed cord. A large dental burr—use by dentists, not for teeth, but for trimming vulcanite, etc.—is helpful in removing dense bone gently. Incidentally perivertebral abscesses are cleared out.

INDICATIONS FOR OPERATION.—From our experience we propose four principal indications: (1) A rapidly progressive paraparesis which is advancing daily and is nearing total paralysis. In these acute cases there is grave danger of acute ischæmia of the compressed cord and irrevocable damage of it. I feel it is unjustifiable to risk valuable hours on attempts at "conservative" treatment. I am willing to operate at midnight on these cases—every hour may be so vitally important. One should not take the risk of procrastination; one should *see* without delay that injurious pressure is removed from the theca.

(2) The case in which paraparesis advances over weeks or months in spite of effective fixation and postural correction. Here again, one must not permit the paraparesis to advance too far, lest permanent damage be done to the cord and an incomplete or unduly delayed recovery result. There is not the same element of urgency as in the first group.

(3) The chronic case in which, in spite of adequate fixation and postural correction, even a slight or moderate paraparesis develops and persists.

(4) Those cases in which adequate fixation is made impossible by spontaneous spasms of the paretic parts. This sets up a vicious circle already referred to, which leads to an extremely miserable death, and which can only be broken by rapid and effective decompression of the cord. A rather similar indication can arise from visceral derangements dependent on the paralysis. One of our patients was tried five times at intervals of a few days on well-constructed posterior and anterior shells. Each time severe meteorism made it necessary to release her. She was then decompressed and there was no further difficulty in postural management.

## RESULTS

There have been 3 *deaths* in the 18 cases operated on. (1) One must be regarded as non-recurrent from a statistical point of view. In that unfortunate young woman's case we had already carried out a

left lateral decompression before the anterior technique was developed. After brief improvement her spinal cord functions deteriorated, and we then carried out our newly developed anterior operation on the right side. This had the unfortunate effect of dividing pedicles on both sides and of dissociating the neural arches from vertebral bodies. This led to such instability that deformity rapidly increased and the cord was crushed. Such an error will not be made again. She died after a long illness from urinary and bedsores complications of paraplegia. (2) The second death occurred 40 hours after operation from uræmia as principal cause. The woman, aged 45, had a rapidly advancing paraplegia, and perhaps in face of this urgency insufficient time was taken to assess her general state. At post-mortem examination early miliary disease was found, the kidneys being somewhat heavily invaded.

(3) The third death occurred 70 hours after operation, also from uræmia. The patient, aged 65, was arteriosclerotic and hypertensive, but in face of a rapidly advancing paraplegia we decided to attempt to help him. The immediate effects of operation precipitated renal failure.

*Failure.*—One patient with a 90° kyphosis of 26 years' standing, sclerosed bone at the mid-dorsal site of disease, and with a slowly advancing paraparesis which had reached severe grade, had his cord damaged in the process of decompressing it. His paralysis was aggravated and has not recovered to a significant degree. This is the only disaster in addition to the three deaths. We learned to use the dental burr after this misfortune and we feel it is a tragedy unlikely to recur.

*Post-operative Complications.*—As just mentioned, 2 patients died of uræmia. Two others, who eventually recovered well, exhibited an acute post-operative nephritis—one, a boy of 9 with considerable tuberculo-toxæmia; the other a man of 32 with chronic sclerosed disease and apparent good general health. Apparently the kidneys require special safeguarding and care when a major operative procedure for Pott's paraplegia is to be undertaken.

There have been many minor complications in the care of these cases—especially before spinal cord recovery is well under way. These mostly concern nursing management. They have certainly been minimised by our increasing use of skeletal traction technique.

*Cord Recoveries.*—When we turn to the credit side of the balance we find it far outweighs the debit.

No less than 12 of the 15 survivors of our 18 operated cases have achieved *complete recovery* of spinal cord functions. When I say complete, I mean complete as judged by the most exacting standard. *Two* are *nearly complete* in cord recovery, *i.e.* their spinal cord state is compatible with normal activity but not with athletic performance. One of these is a recent case and will probably join the company of complete cord recoveries. *One* case, whose kyphosis was extreme and whose severe

paraparesis was of 9 years' standing, has recovered only *partially*. She has efficient bladder control and will probably become ambulant with aid of crutches.

When the serious nature of most of the cases we have dealt with is considered—the failure of conservative treatment in most of them, the failure of other operations on some of them, the fact that no case with a shadow of a chance of recovery has been rejected as a candidate for anterior decompression—not even a severe paralysis of 9 years' duration, nor an arterio-sclerotic man of 65 years of age—a complete cord recovery rate of 67 per cent. and recovery to a good ambulatory level in 78 per cent. is encouraging and creditable.

In addition to the operation cases, the 3 patients treated by *traction only*, as a supplement to recumbency on a shell, have each recovered normal spinal cord function.

Cord recovery is usually rapid at first. In a few cases it has been complete in the first few weeks. In the more chronic cases, after a rapid early improvement final recovery may extend over a year or more. But they are comfortable. They have already regained sphincteric control, and their sense of security.

*Recovery of Spinal Fluid Block.*—In all cases where partial or complete spinal fluid block was present before treatment, it has cleared after treatment conformably with cord recovery. In some cases fluid passage is restored already as the operation is completed.

*Recovery of General Health.*—Improvement in general health has been striking and usually rapid after operation. There has been no suggestion of dissemination of disease or exacerbation of toxæmia. On the contrary tuberculo-toxæmia has at once diminished—due no doubt to the relief of pressure in abscesses. All the visceral and infective ills that accompany paraplegia have been relieved with corresponding improvement in general health.

*Vertebral recovery.*—With our longest cases under 3 years from operative treatment it is too early to express a decisive view. So far, I think, the operation makes little difference to bone recovery, other than by improving general health. There is no evidence that it has any adverse effect. I anticipate that removal of remnants of disc cartilage at the diseased site may favour the eventual consolidation of sound bone. Skeletal traction has certainly been of great value in diminishing the degree of deformation.

The atlanto-axoid case with early bone grafting after reduction may be regarded as cured. Another lower dorsal case was immobilised for 2 years 2 months and was grafted at 1 year 2 months after our operation. She is ambulant and was sent home recently.

Most of the others are still under hospital care. There have been some minor setbacks. One little girl with cervico-dorsal disease, treated by skeletal traction only, had some recurrence of cord compression at the 11th month due to an insufficiently extended position provided by a new shell. Correction of this and reapplication of

skeletal traction for  $2\frac{1}{2}$  months has restored cord function completely. Two of the operated cases have had subsequent vertebral setbacks—but in neither of them has this affected cord function. One a chronic, sclerosed lower dorsal lesion, was immobilised for 18 months after decompression and then allowed up. Local vertebral pain and a fresh erosion in a vertebral body followed. He was immobilised again and bone-grafted and continues well. One with cervico-dorsal disease of active erosive type was bone-grafted 7 months after decompression. This graft—probably too early—has not held, and on removing the shell at 16 months the deformity has increased. Further traction correction and further grafting will be required. But the important point is that her spinal cord remains intact.

Three of our cases have sinuses from former operations, 2 similar sinuses have healed. Two of our 15 cases have developed sinus at the site of the anterior decompression wound. One broke through 18 months after operation—it now discharges very little. The other—an acute case with abscess already in dorsal muscles at time of operation, broke through 3 months after operation.

I should think most of our cord-recovered cases will benefit and gain in security by bone-grafting at an appropriate period of convalescence; but that is a matter for the professional orthopædist and tuberculosis expert rather than myself.



## ANTICOAGULANTS \*

By Professor J. R. LEARMONTH, *C.B.E.*, Ch.M., F.R.C.S.E.  
Department of Surgery, University of Edinburgh

I APPEAR to-night in an unorthodox rôle as someone who has spent most of his life trying to stop bleeding, but who is now advocating measures to make the blood incoagulable in certain conditions.

Macfarlane has pointed out that whatever the size of the wounded vessel or vessels, control of hæmorrhage is brought about by the operation of two different processes : (1) contraction of the vessel concerned, after a preliminary immediate dilatation, and (2) coagulation of the blood escaping from the wounded vessel. It is with the second of these problems that to-night's discussion deals.

The time-honoured explanation for the coagulation of blood is set out in the familiar two equations :—

(1) Prothrombin +  $\text{Ca}^{++}$  + thrombokinase = thrombin.

(2) Thrombin + fibrinogen = fibrin.

Coagulation time depends on the rate at which reaction (1) proceeds, not on the total quantity of prothrombin present. The equations are not quantitative but qualitative, and express only a part of the rôles played by the various substances concerned. It is particularly to be remembered, as Macfarlane has also pointed out, that the coagulation time as measured in the laboratory depends upon the rate at which reaction (1) proceeds, and is not greatly influenced by the total quantity of prothrombin present in the blood until this has been reduced to extremely low levels. Macfarlane prefers to consider the problem in the light of a system in constantly shifting equilibrium, in which the various substances may have other functions, notably perhaps metabolic functions, in addition to their more striking function of playing a part in the arrest of hæmorrhage.

Since blood will clot in test tube after its abstraction from a vessel with the minimum of trauma, Macfarlane holds that it contains a substance, prokinase, which in contact with a water-wettable foreign substance is transformed to kinase which will set the first equation in operation. In ordinary circumstances, the greater part of the kinase necessary is liberated from tissues damaged by the trauma which has resulted in bleeding. The action of prokinase in the normal blood stream is prevented in two ways :—(1) the vascular endothelium is not wettable, and (2) the circulating heparin has an antikinase action. Prothrombin is manufactured in the liver, and for its supply in adequate quantities a normally functioning liver is essential, together

\* Read at a meeting of the Medico-Chirurgical Society of Edinburgh, on 9th July 1947.

with a supply of vitamin K. For the proper manufacture and absorption of vitamin K in ordinary circumstances, bile salts, a healthy intestinal tract and bacteria in the intestinal tract are necessary.

When the first reaction has operated, the thrombin that is formed acts on fibrinogen, also manufactured in the liver, and precipitates this albuminous substance in the form of long needle-like crystals, contraction of which in the course of time produces the well-known retraction of the clot and expression of serum from its interstices.

If one wishes to prevent the coagulation of blood, either *in vitro* or *in vivo*, there are certain possible procedures which vary according to the phase of the process which it is desired to interrupt. These various procedures are shown in the Table :—

TABLE

*Prevention of Coagulation*

*Phase 1.*—Thrombokinase +  $\text{Ca}^{++}$  + prothrombin = thrombin.

- (1) Collect blood in non-water-wettable receptacle :—
  - (a) Paraffin lined flask.
  - (b) Amber (athrombit vessel).
  - (c) Lucite vessel.
- (2) Remove calcium ions :—
  - (a) By precipitating as insoluble oxalate.
  - (b) By substituting non-ionizable calco-citrate.
- (3)
  - (a) By reducing amount of prothrombin by giving dicoumarin.
  - (b) By antiprothrombic action of heparin.

*Phase 2.*—Thrombin + fibrinogen = fibrin.

By the antithrombic activity of heparin, in the presence of serum antithrombin and neutral salts.

To-night we are concerned with those in the third group, that is all those which act in the living body, which are designed to make blood incoagulable in the vessels or when shed. We have had most experience with heparin, which is probably derived from the granules of mast cells, which are widely distributed in the animal kingdom around the walls of vessels and in the subcutaneous tissues. This substance has certain properties : (1) it is a neutraliser of thrombokinase and may play some part in maintaining the normal fluidity of the blood circulation. (2) It is an antiprothrombin. It may thus interfere both with the preliminaries to the first reaction and with the course of the reaction once the factors concerned in that reaction are present. It must be noted that its action as an antiprothrombin may be neutralised by an excess of thrombokinase. (3) In the presence of plasma and neutral salts heparin acts as an antithrombin. Normally an antithrombin is present in the serum albumin fraction of the blood proteins. When the normal process of clotting is initiated, thrombin prefers fibrinogen to this serum antithrombin, but when heparin is added to the mixture either *in vitro* or *in vivo*, the complex (serum antithrombin plus neutral salts plus heparin) competes with thrombin for the fibrinogen and so prevents the second phase of the process of

coagulation. Heparin appears to act in a physico-chemical manner in virtue of the very large negative electrical charge which it carries, since it is a strong acid. Chemically it is mucoitin polysulphuric acid. A knowledge of this physico-chemical process, which we owe to Jorpes who has also elucidated the chemistry of heparin, has provided a method of immediately neutralising its action *in vivo*. This consists in the injection of a solution of protamine sulphate, which carries a high positive electrical charge which discharges the negative charge on the heparin and thus brings its activity to an end.

Dicoumarin, on the other hand, was first identified as the substance in spoiled clover which causes hæmorrhagic disease in cattle. It can now be synthesised and given by mouth. It appears to act by diminishing the ability of the liver to produce prothrombin and possibly also fibrinogen, but it has no direct action upon prothrombin and therefore its effect is delayed until the prothrombin circulating in the blood has been used up by metabolic processes. Since it acts as an hepatic poison, its use is not altogether devoid of risk.

These two anticoagulant substances provide us with means whereby the blood can be immediately rendered incoagulant (heparin) or interference with coagulation may be delayed (dicoumarin), the extent of the delay varying from twenty-four to seventy-two hours according to the state of the liver and the dose of dicoumarin. This is not an altogether complete statement because in certain conditions, and notably in thrombo-angiitis obliterans where the obstruction of vessels by thrombi is an important part of the pathological process, certain patients may display a resistance to both heparin and dicoumarin, which may modify the dosage required and which lends emphasis to the point, that any patient under anticoagulant therapy should be treated in surroundings which permit of regular accurate estimates of either the coagulation time (heparin) or the amount of prothrombin (dicoumarin) in the blood.

The factors which tend to produce pathological clotting in the vessel may be summarised under three heads:—(1) slow circulation; (2) increased coagulability of the blood (hypoproteinæmia, hyperglobulinæmia, increase in fibrinogen, polypeptide, peptidase, and calcium, acceleration of the sedimentation rate, exaggeration of the tendency of the platelets to agglutinate, and, if dehydration has occurred, increased viscosity of the blood: thrombokinase); (3) injury to intima. Even when, so far as possible clinically, each of these factors has been avoided or corrected, a thrombus may occur post-operatively after parturition, as a complication of certain acute fevers, after injury and in the course of certain diseases such as thrombo-angiitis obliterans. Occasionally also thrombosis appears to be spontaneous and not to be associated with any of the factors which I have enumerated. Anticoagulant therapy may thus be required in one or both of two sets of circumstances: (1) prophylactic, which is employed when the circumstances are favourable for thrombosis or

when a patient is known to have had thrombosis after a previous operative experience. Obviously the best example of this applicability is following operations upon blood vessels such as arterial suture, when the stage is set for the occurrence of thrombosis at the site of intimal damage. (2) Therapeutic, when thrombosis has already occurred and it is desired to prevent the spread of the thrombus into major blood vessels, either arterial or venous, with a view to preserving the maximum number of collateral channels or, if the thrombosis affects veins, of preventing the clot reaching a major vein in which a portion of it may be swept away to form a pulmonary embolus. The details of these two methods of employment will be dealt with by the subsequent speakers.

## ANTICOAGULANTS \*

By C. C. BURT, B.Sc., M.B., Ch.B.

### HEPARIN—METHODS OF ADMINISTRATION AND CONTROL OF DOSAGE

FROM 1935 onwards, clinical trials of heparin were carried out by Crafoord (1937, 1939) in Sweden, and by Murray and his co-workers (1936, 1938*a* and *b*) in Toronto. Crafoord relied on the method of intermittent intravenous injection three to four times a day (100, 100, 150 mgm.), and later Swedish workers have largely adhered to this procedure, whereas the Toronto workers preferred continuous administration by means of an intravenous drip.

A single intravenous injection of heparin acts immediately, and blood withdrawn within five minutes of administration may not clot for several hours. The effect, however, passes off rapidly, and clotting time has usually returned to normal three hours after an intravenous injection. This means that when the intermittent intravenous method is used, the patient's clotting time may be normal for perhaps twelve out of twenty-four hours, whereas by continuous drip it is possible to maintain the clotting time at any desired level (usually that chosen is twelve to fifteen minutes). Murray and Best (1938*a* and *b*) used a saline solution containing 10 mgm. (1000 units) heparin for each 100 c.c. of solution, and regulated the drip to run at about 25 drops per minute, but the heparin can also be added to glucose, plasma or blood.

Reports by Swedish workers on results of treatment of thrombotic disease by the method of intermittent intravenous dosage are comparable with those of Canadian and American workers using the continuous drip method, so that contrary to what one might expect, the thrombotic process apparently does not spread to any significant extent during the short periods of normal clotting time which occur when the intermittent method is used.

As yet there is no preparation of heparin which is effective if administered by mouth, but last year Loewe and others (1946) reported prolongation of the effects of heparin by combining it with a menstruum containing gelatine, dextrose and glacial acetic acid, with or without a vasoconstrictor substance. This mixture could be given deeply subcutaneously, and the authors stated that a single injection containing 300-400 mgm. of heparin (30,000-40,000 units) would result in elevation of the clotting time for two days. Swelling, pain and tenderness at the site of injection and fever were, however, reported in some cases following this treatment.

\* Read at a meeting of the Medico-Chirurgical Society of Edinburgh, on 9th July 1947.

In the majority of cases reported to-night the method of intermittent intravenous injection three times a day was adopted (44 out of 61), but in 6 of these the drug was also given for part of the time by the intramuscular or deep subcutaneous route.

The dosage given was based on that advocated by the Swedish workers, 5000-15,000 units being given as an initial dose (100 units = 1 mgm. of crystalline barium salt of standard purified heparin). The actual amount of the initial dose varied according to the patient's size, and subsequent doses were regulated according to the response to heparin as measured by the clotting time. The capillary tube

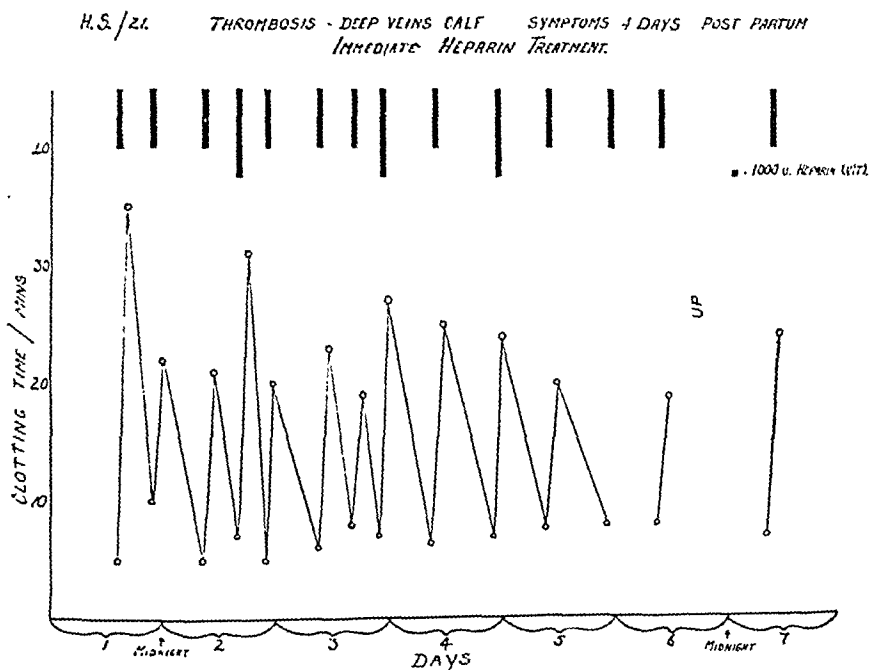


FIG. 1.—H.S./21. The graph shows the clotting time recorded immediately before and one hour after each injection of heparin during the first five days of treatment. This patient was allowed up on the sixth day and heparin was discontinued on the seventh day.

method of estimating clotting time was used as a routine. This gives a normal range of approximately four to eight minutes. It is not an accurate method, but was satisfactory in so far as no unexpected bleeding occurred in any patient in whom the clotting time had been estimated to be within the normal range. Fig. 1 shows a record of the dosage and clotting time estimation in the case of a patient with a deep venous thrombosis. We found that estimation of the clotting time immediately before each injection, and one hour after, was sufficient, and a rise to fifteen minutes or over was regarded as an adequate response.

Satisfactory rises in clotting time were obtained with three different preparations of heparin given by the intramuscular or deep subcutaneous

route: when plotted the curve closely paralleled that of the clotting time following intravenous injections, but in one or two instances the rise was smaller and slower, taking three hours to reach a therapeutic level. One of these preparations contained only 1000 units per c.c. and we had previously avoided giving it in this way because of the bulk of the injection, 5-7½ c.c. as against 1-2 c.c. of the other preparations, as it was thought that this might lead to formation of a hæmatoma. Following subcutaneous administration of all types of heparin, small areas of bruising appeared, but none of the patients complained of discomfort, and no other ill effects became evident.

The continuous intravenous drip method was used in 8 patients, 7 of whom had had operations on blood vessels. In 4 of these, heparin therapy was started towards the close of the operation, a boosting initial dose of 5000 units being given and the drip thereafter regulated to keep the clotting time as near twelve to fifteen minutes as possible. In the other 3 patients (lieno-renal anastomosis) heparin therapy was begun six hours after operation. In operations on blood vessels, 4000-6000 units of heparin were added to 400 c.c. of transfusion fluid, and treatment was maintained for periods varying from fifteen and a half hours to twelve days. In the 3 cases of lieno-renal anastomosis, 2500-4000 units of heparin per 400 c.c. transfusion fluid were used, and treatment was maintained for one to four days. The total amounts of heparin used in these cases were 10,000-292,000 units.

Initial resistance to heparin, as shown by failure of the clotting time to rise to a satisfactory level during the first day, was encountered in 3 patients. One of these was a girl of twenty-two with a spontaneous axillary vein thrombosis, and another an old lady of seventy-one with a popliteal embolus. The third was a woman of thirty-six who was admitted to Professor Learmonth's ward with an aortic embolus following a gynæcological operation, and who had previously had two small pulmonary emboli. Towards the close of the embolectomy operation, she was given 5 c.c. of heparin intravenously under the mistaken impression that the solution contained 1000 units of heparin per c.c., whereas actually the strength was 5000 units per c.c., so that the total dose was 25,000 units. In spite of this her clotting time did not show a rise until six hours later, during the last four of which a continuous intravenous heparin drip (5000 units to the pint) had also been running. Prolonged resistance to heparin was found in one patient with thrombo-angiitis obliterans, who will be referred to later (Fig. 4) as he failed to respond to dicoumarin therapy also.

Prolonged elevation of clotting time following single intravenous or intramuscular injection was seldom encountered in this series, but in one girl the clotting time was fifty minutes, five hours after intravenous injection of 7500 units (Swedish) heparin and over twenty minutes, seven hours after intramuscular injection of the same amount. It was normal ten hours after injection.

## DICOUMARIN—METHODS OF ADMINISTRATION AND CONTROL OF DOSAGE

Dicoumarin, which is given by mouth, is simpler to administer than heparin, but less easy to control because of the large individual variation in rate and amount of response to it. In our series, on the first day 300 mgm. were usually given, followed by 100-200 mgm.

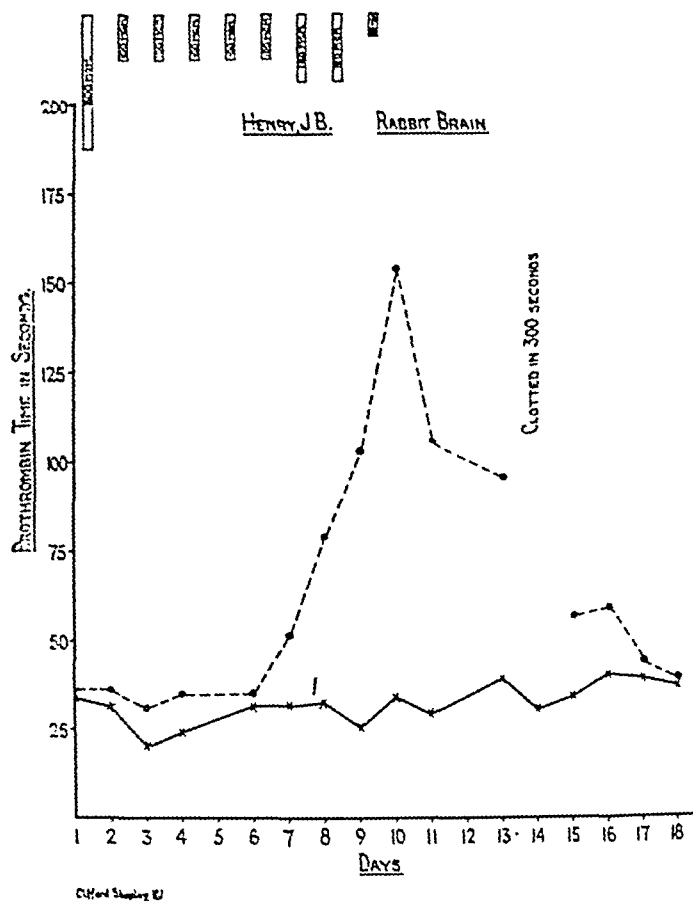


FIG. 2.—J.B.H. A patient with a spontaneous deep venous thrombosis treated by dicoumarin therapy. The daily dosage of dicoumarin in milligrams is indicated at the top of the chart. Control prothrombin times varied between twenty-five and forty seconds and are indicated by the continuous line, while the dotted line shows that the patient's prothrombin time did not rise significantly until the seventh day of treatment. There was a similar delay in fall of prothrombin time at the close of treatment.

on the second day, and thereafter the amount was regulated by the effect shown on the prothrombin time. I do not propose to deal with methods of estimating prothrombin time, but briefly they consist of inducing accelerated clotting of oxalated plasma by the addition of excess thromboplastin and calcium which eliminates the possibility of interference with clotting due to their lack or short supply. The rate of clotting then varies inversely with the amount of prothrombin



present. As dicoumarin prevents formation of prothrombin, the amount present in the dicoumarinised patient becomes diminished and the prothrombin time is increased above that of normal plasma. By estimating the prothrombin times for various dilutions of plasma, Quick (1937) worked out a graph which indicates the prothrombin time corresponding to the various percentages of prothrombin. In thrombo-embolic disease reduction of prothrombin to between 10 and 30 per cent. of normal is considered to be of therapeutic value, and Allen *et al.* (1942, 1945 and 1946) report that they have maintained

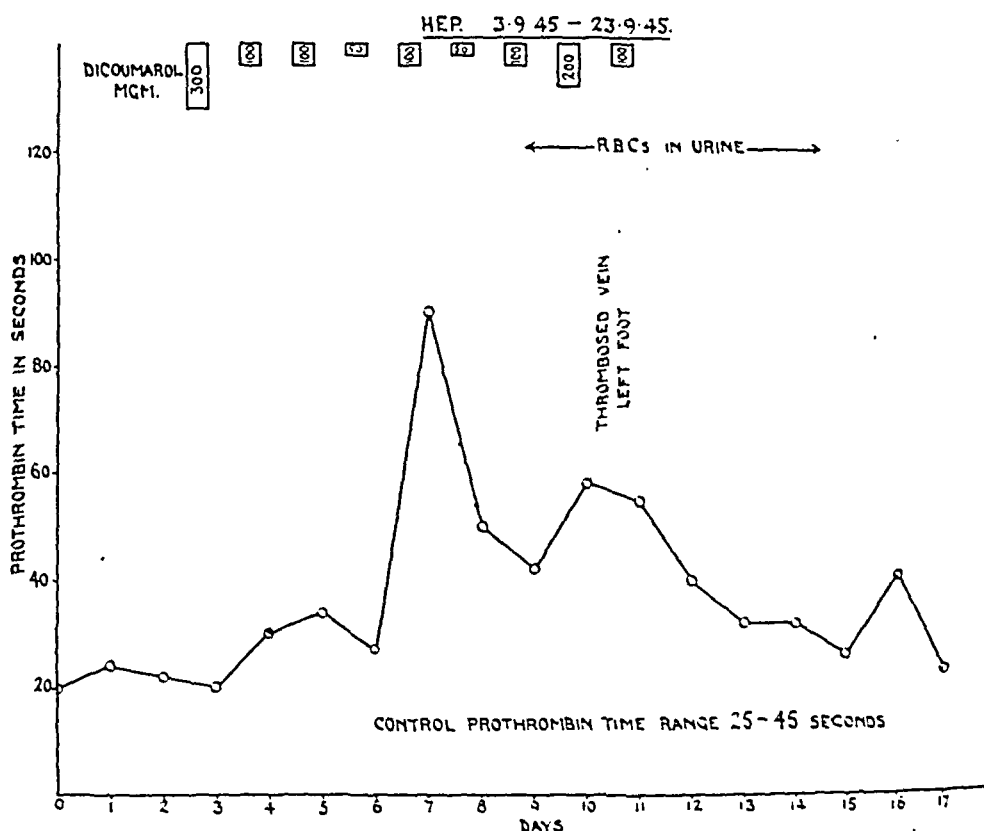


FIG. 3.—H.E.P. This shows the graph of the prothrombin time estimation in the case of a patient with thrombo-phlebitis migrans treated with dicoumarin. Haematuria appeared while the prothrombin time was still within the normal range, and further thromboses of superficial veins were also noted during this period. Dicoumarin treatment was discontinued because of frank haematuria.

prothrombin at these levels for as long as six months without ill effect. They emphasise, however, that the patient must be in hospital or under daily medical supervision, and that daily prothrombin tests must be done. Dicoumarin alone was used in 11 of the present series and in conjunction with heparin in 6 others. The maximum total dose given in one course was 2275 mgm. during forty-three days, and in all cases an attempt was made to keep the prothrombin percentage between 20 and 60 which is possibly not low enough. The time taken for the prothrombin time to rise to the required level in our series varied between forty hours and seven days after beginning

treatment, and it returned to normal in from one to seven days (Fig. 2). We also considered it advisable to examine the urine daily for red blood cells. Hæmaturia occurred in one patient, who, judged by prothrombin time, was apparently resistant to dicoumarin (Fig. 3). Resistance to combined heparin and dicoumarin therapy was seldom encountered, but Fig. 4 shows failure to respond to the usual doses in the case of a man with thrombo-angiitis obliterans.

### CONTROL OF BLEEDING

(a) *In the Heparinised Patient.*—If bleeding occurs in a heparinised patient, administration of heparin should be stopped forthwith.

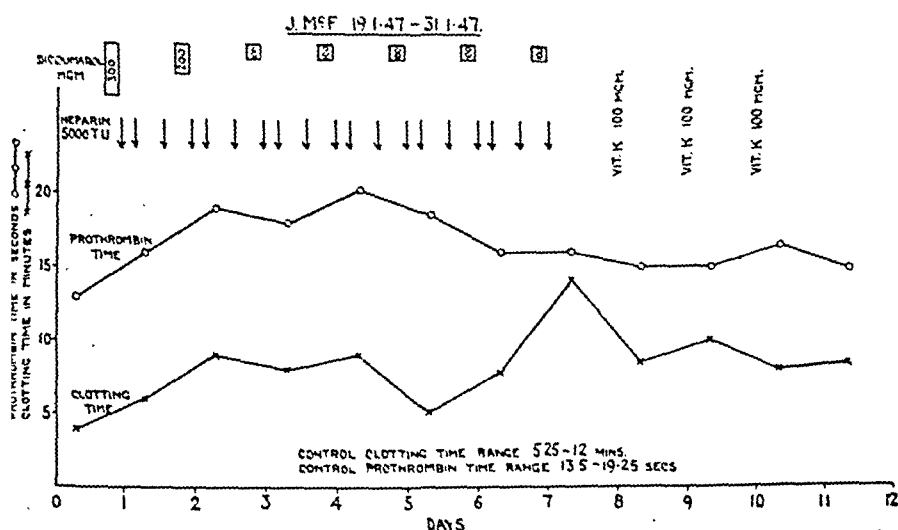


FIG. 4.—J.McF. In this chart little effect on clotting time or prothrombin time is shown from combined heparin and dicoumarin therapy in the case of a patient with severe thrombo-angiitis obliterans. Note that the control prothrombin range in this case is lower than that indicated in the previous figures. This was due to the adoption of a different method of prothrombin time estimation.

Professor Learmonth has dealt with protamine sulphate which is a specific and immediate antagonist of heparin. We found it necessary to use it in only one case (hæmatemesis following lino-renal anastomosis). One c.c. was injected into the drip tubing after normal saline had been substituted for the heparinised solution the patient had been receiving. Blood should be given if thought necessary: if there is oozing from an exposed raw area, local application of stypven or thrombin may suffice. In any case, the effect of the heparin should have passed off in two to three hours. Oozing from the wound and probably some intraperitoneal bleeding occurred during the first twenty-four hours following operation in one of our heparinised patients. Blood was substituted for the heparinised solution in the drip, and he did very well although his wound healed slowly. Formation of a hæmatoma, which necessitated opening the wound and removing the

clot, occurred in one patient on post-operative intermittent heparin therapy following exploration of a thrombosed popliteal artery.

One point of interest has arisen during this work which is of importance in patients who may be having massage or who run the risk of trauma during heparin treatment. Hæmorrhage into the right rectus muscle was noted at autopsy in an old lady with auricular fibrillation who died following repeated embolic episodes which had not been averted by heparin therapy; in two patients with deep venous thrombosis in the leg, bruising followed deep palpation in one and massage in the other. It is possible that minor trauma to small vessels may result from these procedures, and if the patient is fully heparinised at the time, excessive bleeding may occur and later become manifest as bruising. In the unit it is now arranged that patients who are having massage and heparin therapy are given the massage either before the morning dose of heparin or not until two to three hours after this dose.

(b) *In the Dicoumarinised Patient.*—The prolonged action of dicoumarin makes hæmorrhage in a dicoumarinised patient more difficult to control than in the case of heparin. There is no specific antidote with an immediate action, but vitamin K in large doses—200 mgm.—has a slow antagonistic action. If hæmorrhage is severe, repeated transfusion of fresh blood may be necessary and thrombin applied to a localised bleeding surface, if such is present, may temporarily help matters. It is necessary to emphasise that a patient who bleeds while on dicoumarin therapy will need careful watching for days.

No effect was noted on menstrual flow during heparin or dicoumarin therapy in our series nor did the lochia appear to be increased, but during the puerperium the third was the earliest day on which heparin was given.

## DISCUSSION

In the present series anti-coagulants were used as therapeutic agents in 61 patients. Nineteen of these had thrombo-embolic phenomena following childbirth and are being discussed by Dr Matthew. The conditions and treatment in the other cases are shown in the Table.

The numbers are too small and the conditions and extent of symptoms too varied for any definite conclusions concerning the value of anticoagulant therapy to be drawn in this series, but one or two points of interest may be mentioned.

(a) *Effect on Pain.*—Four patients with severe pain following acute arterial occlusion in the limb reported a rapid and marked analgesic effect of intravenous injection of heparin. One, a physician who had had very severe pain for eight days following thrombosis of his popliteal artery, stated that the relief following intravenous heparin was greater than that following morphia. It occurred within

five to fifteen minutes and lasted up to nine hours. Another patient reported similar rapid relief, but for a shorter period—two to two and a half hours—and the other two patients were more indefinite concerning times although certain that relief occurred. Intravenous administration of heparin (7500 units) to two normal adults did not produce any increase in hand blood flow, so that it is unlikely that the analgesic effect can be due to vasodilatation.

In the cases of deep venous thrombosis, relief of pain or discomfort followed in about twenty-four hours after start of heparin therapy, and may have been due to diminution of swelling and tension resulting from elevation of the limb rather than to heparin alone.

(b) *Arterial Thrombosis or Embolism.*—Only 3 patients with arterial occlusion due to thrombosis or embolism were admitted within

TABLE

Condition.	Treatment.		
	Heparin.	Dicoumarin.	Heparin + Dicoumarin.
During and following operations on blood vessels :—			
lienorenal anastomosis, 3	8	...	...
thrombosis or embolism, 5			
Acute arterial thrombosis and/or embolism	3	...	2
Femoral thrombosis (toxic) late	1	...	...
Thrombosis (arteriosclerotic)	1	2	2
Post-operative venous thrombosis	5	...	...
Venous thrombosis in puerperium	18	...	1
Idiopathic venous thrombosis	6	2	...
Pulmonary embolism	1	...	...
	(+3)		
Thrombo-angiitis obliterans	...	5	1
Thrombo-angiitis obliterans + migratory phlebitis	1	2	...
Total	44	11	6

twenty-four hours of onset. Aortic embolectomy was performed by Professor Learmonth on one with a successful result. Extensive thrombosis proximal and distal to a thrombosed popliteal aneurysm was found at operation in the second patient, and amputation was ultimately performed. The third was the case of auricular fibrillation, who has been mentioned already. As might have been expected, heparinisation failed to prevent further embolic episodes. At autopsy the auricle did not contain any residual clot.

In other cases irreversible changes had occurred before admission, and the most that could be hoped for was prevention of proximal extension of thrombosis. This effect is well illustrated in the case of a school cleaner who developed sudden severe pain in the right index finger while washing a floor. Pain continued for several days and the patient described typical vasospastic attacks in the index finger. When she was seen ten days later, the tip of the index finger was gangrenous. X-ray of the cervical spine disclosed bilateral

cervical ribs; her right subclavian artery was grossly dilated, and pulsation was palpable in the subclavian, brachial and radial arteries. It was considered that a small embolus had been dislodged from a mural thrombus in the subclavian artery and had blocked a digital vessel. A course of heparin and dicoumarin therapy was instituted and following this the right cervical rib was resected. When she reported two months after discharge from hospital, the nutrition of her hand was good.

The results in post-operative venous thrombosis and idiopathic thrombosis were satisfactory and good results also followed heparin therapy in the one case of pulmonary embolism treated in Professor Learmonth's wards during the past year. This was a severe case which developed ten days after lumbar sympathectomy without any premonitory signs or symptoms. Intermittent intravenous heparin treatment plus sulphanilamide and penicillin were given. The patient made steady progress and was discharged home three weeks later. After seven days of heparin treatment, it was noted that blood-staining of the sputum was very profuse and this continued, gradually diminishing, until he was discharged.

Migratory phlebitis in one case of thrombo-angiitis obliterans was quickly relieved following heparin therapy, while dicoumarin therapy had no effect on two other patients with the same condition, nor had it any effect in preventing extension of the pathological process in the other cases of thrombo-angiitis obliterans treated. It is possible, however, that dosage was inadequate.

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## THROMBO-PHLEBITIS IN PREGNANCY \*

By G. D. MATTHEW, F.R.C.S.E., M.R.C.O.G.

ALTHOUGH the incidence of thrombo-phlebitis and pulmonary embolism following delivery is no greater than that following general surgical procedures it seemed wise to deal with this subject separately because of the peculiar features exhibited by this condition in the obstetric patient. But the main reason for the presentation of an obstetrical paper to this Society is that Professor Learmonth has extended his interest in heparin therapy to include the Simpson Memorial Maternity Pavilion where he and Dr Burt have supervised the treatment of several cases during the past year. It should be noted at this point that venous thrombosis is not entirely restricted to the post-partum phase of pregnancy, although much more common at this time, for occasional cases of both thrombo-phlebitis and pulmonary embolism do arise during the antenatal period. In the Simpson Maternity Pavilion the over-all incidence of these two conditions is in the region of 1 per cent. and this figure agrees closely with published figures, and also with the incidence following surgical operations. As in gynæcological pelvic operations, however, the incidence rises in Cæsarean section to about 4 per cent. and to an even higher level in high forceps deliveries.

During the past twenty years there have been 17 recorded deaths in the Simpson Maternity Pavilion from that lethal associate of thrombo-phlebitis, pulmonary embolism, and it may well be that other cases diagnosed as pneumonia may have had an underlying embolic origin. Although this total is perhaps surprisingly low, it means that one maternal death per annum may be expected from this source alone. This statement, of course, refers to hospital practice, where methods of delivery, other than spontaneous vaginal, are commonly employed. So any effort directed towards the prevention or rapid control of thrombo-phlebitis is particularly welcome in the hope that not only will this life be saved each year but also that the incapacity associated with the condition will be reduced to a minimum. Perhaps heparin therapy will provide the fulfilment of this hope.

### PREDISPOSING FACTORS

Although Professor Learmonth has dealt very fully with the various factors contributing towards the development of thrombo-phlebitis I feel that there are one or two points which must be mentioned

\* Read at a meeting of the Medico-Chirurgical Society of Edinburgh, on 9th July 1947.

when considering this condition in so far as it affects the pregnant woman. The common finding of a speeding up of the blood sedimentation rate during pregnancy is associated with an elevation of plasma fibrinogen and the part played by this substance in clot formation is clearly established. A degree of venous stasis of the lower limbs occurs in pregnancy as the result of mechanical pressure on the pelvic veins by the growing uterus, and increased volume of venous return to the iliac veins. This effect is likely to be more marked in cases of excessive distension of the uterus as in hydramnios or multiple pregnancy. Evidence of this is seen in the frequent development of varicosities in the veins of the legs and vulvar region, and the equally common but more uncomfortable occurrence of hæmorrhoids. It is usually in varicose veins that the occasional case of thrombo-phlebitis during the antenatal period occurs. The immobilisation of long periods in bed also causes slowing of venous return and this may be aggravated by the associated direct pressure on the veins of the legs. It was perhaps partly on account of these factors that pulmonary embolism occurred fourteen to twenty-one days after delivery either by Cæsarean section or difficult forceps in many of the fatal cases already mentioned. It is generally agreed that injury affecting the intimal coat of the vein plays a part in the development of thrombosis in some cases, and there is no doubt that minor trauma, affecting superficial veins of the legs, must be a distinct possibility as a result of the manipulations and contortions associated with the undignified process of childbirth. Whilst the majority of cases of thrombosis are of a non-inflammatory nature, there is no doubt that infection plays an active rôle in some instances. Unfortunately, this factor must always be considered as a possibility in obstetrics, where the occurrence of sepsis within the pelvis following delivery remains an all too frequent complication. So much, then, for a very brief résumé of some of the predisposing factors which might lead to the development of thrombo-phlebitis in obstetric patients.

### SITES

The location of veins involved by thrombo-phlebitis is essentially the same in obstetric and non-obstetric patients with the exception of the deep pelvic veins. Thus there is involvement of the superficial or deep veins of the calf, the popliteal region or the thigh either individually, successively, or concurrently and affecting either limb or both. In the recently delivered woman the pelvic veins are liable to be the site of involvement. At the end of labour the large venous sinuses of the uterus, and particularly of the placental site, are obliterated by blood clot and if infection occurs, especially by anærobic streptococci, a process of septic thrombo-phlebitis is initiated which may spread through the wall of the uterus to involve the ovarian and uterine veins. In this way there is established a deep pelvic thrombo-phlebitis,

a condition which is not always clinically obvious and thus may account for some cases of apparently unaccountable pulmonary embolism. By further extension the thrombotic process may come to involve the internal iliac and common iliac veins and even the inferior vena cava. Moreover, either by an advancing periphlebitis or possibly by spread along the venous wall, the external iliac and femoral veins may be the site of continuous or isolated areas of thrombo-phlebitis. At this point I feel compelled to refer to the controversial subject of the "White Leg" or to give it the old name—Phlegmasia Alba Dolens. This is neither the time nor the place to enter into a detailed discussion of the possible mechanisms in the development of this condition, which is seldom encountered nowadays, therefore I will dismiss the matter in the speediest possible manner by stating that, in my opinion, ilio-femoral thrombosis is the principal underlying factor but that, in some cases at least, cellulitis and blockage of the perivenous lymphatics also play a part.

### PULMONARY EMBOLISM

Pulmonary embolism, fatal or non-fatal, may occur either before or after thrombo-phlebitis manifests itself clinically, and in the 17 fatal cases mentioned only 7 showed clinical evidence of thrombosis affecting the veins of the pelvis or lower limbs. In this series there were 3 Cæsarean sections, 3 forceps deliveries and the remainder spontaneous vaginal deliveries. In 7 cases the fatal embolism occurred within the first ten days and in the remaining 10, from the eleventh to the thirty-fifth day following delivery.

Nothing need be said about signs and symptoms as our interest to-night is chiefly centred on therapy, but I have no doubt that the simple test for early recognition of thrombo-phlebitis in the leg, described by Homan, will become as much a routine in obstetrics as in other branches of medicine.

### CONTROL SERIES

For the sake of comparison and control I have examined a series of 50 consecutive cases of thrombo-phlebitis occurring in the Simpson Maternity Pavilion. The type of delivery was spontaneous in 33 cases, by Cæsarean section in 13 cases and by forceps in 4 cases. With regard to method of delivery and site of lesion, this series is reasonably comparable with the smaller group of cases, treated by heparin, to be considered shortly. Of the 50 patients, 7 had been confined to bed for long periods prior to delivery, 5 with pre-eclamptic toxæmia and 2 with cardiac disease. In addition a further 14 patients had rested for several hours each day for some time before labour on account of a complication of pregnancy. There were 3 cases of hydramnios and 1 twin pregnancy whilst 6 patients gave a definite



history of varicose veins during the antenatal period. In 13 patients there was evidence of pelvic infection in the puerperium. In 29 patients thrombo-phlebitis was diagnosed within the first ten days and, in the remaining 21, between eleven and twenty-seven days following delivery. Those patients were treated by various methods of more or less complete immobilisation and with local applications, and the majority were confined to bed for anything up to two weeks after signs and symptoms had subsided. As many patients were the victims of spreading thrombosis or repeated thrombosis in different sites, and 3 were complicated by pulmonary embolism, the total length of time in bed was often very protracted. The average period in hospital following delivery in the series was thirty days. Thus it is evident that thrombo-phlebitis not only threatens the life of the patient but also proves itself a most incapacitating disease which helps to increase the burden on the already over-taxed hospital beds.

### HEPARIN TREATED CASES

Those of you who have anticipated a dramatic announcement on the miraculous effects of heparin treatment in thrombo-phlebitis complicating pregnancy are now faced with bitter disappointment. There are several reasons for this sad state of affairs. Firstly, the number of patients so far treated in this way is very small and I fear that my figures would not withstand a detailed statistical analysis. Then, in many instances, there has been a considerable delay between the diagnosis of the condition and the commencement of therapy. I should point out that this delay has been due to tardiness or hesitation on the part of the obstetrician and not to lack of response by Professor Learmonth who is both prepared and anxious to treat cases at all times at a moment's notice. Another point to note is that this group consists of selected cases, as heparin therapy is not yet the routine treatment in every case of thrombo-phlebitis. Unfortunately, an adequate supply of heparin was not always available and in some cases was insufficient to complete the course of treatment. So far heparin has been used only in the treatment of established thrombo-phlebitis and consequently no effort has been made, with this substance, to prevent the unheralded case of pulmonary embolism. Finally, I feel that complete confidence in this method of treatment has been lacking with the result that patients have been detained in hospital for an unnecessarily long time after control of the disease and abolition of signs and symptoms.

In all, 19 patients have been treated with heparin and of these 16 suffered from thrombo-phlebitis of the veins of the pelvis and/or lower limbs, 9 being regarded as deep and the remainder superficial; 1 had thrombo-phlebitis in the arm following intravenous therapy and 2 were cases of pulmonary embolism. To deal with the group of 16 cases firstly, delivery was spontaneous in 8, by Cæsarean section

in 6, by abdominal hysterotomy in 1, and by forceps in 1. Attention is drawn to the higher incidence of abdominal section in this group as compared with the control series, 41 per cent. as against 26 per cent. Five patients had spent some time in bed prior to delivery, each of these pregnancies being complicated by toxæmia or hypertension, and 2 had shown evidence of varicose veins during the antenatal period. Two cases were complicated by marked hydramnios. All the possible sites of thrombo-phlebitis were involved, individually or collectively, and in 3 women there was clinical evidence of pelvic infection. There was delay, varying from one to six days, in the commencement of treatment following clinical recognition, in 10 patients. All cases rapidly responded to treatment with two exceptions. In one patient with evidence of deep pelvic infection there was a recurrence of deep thrombo-phlebitis, and pulmonary embolism occurred after heparin therapy had been discontinued, apparently prematurely. In the second case, embolism occurred seven days after diagnosis of saphenous thrombosis. Heparin treatment had been instituted early but the supply was inadequate and the course could not be completed. The average duration of hospitalisation following delivery in this heparin-treated group was twenty-three days.

The case exhibiting thrombo-phlebitis of the arm following intravenous therapy was interesting. Spread from the cephalic to the axillary and then to the subclavian and innominate veins of the left side had taken place prior to the institution of continuous heparin, and later of dicoumarol therapy. Spread was quickly arrested and it is certain that the patient owes her life to this form of treatment.

The first case of pulmonary embolism occurred on the sixth day following delivery in a patient who had suffered from varicose veins with phlebitis during the antenatal period. There was no evidence of pelvic infection or thrombo-phlebitis and following heparin therapy there was no recurrence of embolism and the patient was discharged twenty-one days after delivery. The second case occurred on the eighth day following evacuation of the uterus for an incomplete abortion. There was no evidence either of localised thrombo-phlebitis or of pelvic infection, and no recurrence following heparin therapy.

### CONCLUSIONS

I find it very difficult, and indeed consider it unwise, to draw any very definite conclusions from this small series of patients amongst whom treatment was unavoidably inadequate in some instances. However, some comparison between the control and heparin-treated series might give a pointer to the wisdom and value of this treatment. Amongst the objects of heparin therapy are the immediate control of the local thrombosis, the prevention of local spread, the prevention of recurrence in the original site or elsewhere, and the prevention of pulmonary embolism in established cases of thrombo-phlebitis. These

objectives were satisfied in all the cases, with two exceptions. In both of these embolism occurred, in one after premature interruption of treatment and in the other where a full course of treatment was rendered impossible owing to insufficient supplies. One of the main hopes in heparin therapy is a marked reduction in the period of hospitalisation. The average difference between the heparin treated and control series was one week. Particularly in view of the much higher rate of abdomino-pelvic operations this difference must certainly be regarded as significant. With earlier institution of heparin therapy and a greater confidence in its powers, this reduction in time spent in hospital should be further reduced. So much for treatment, but it is obvious that of equal importance is prophylaxis for only by this approach can the more dangerous condition of pulmonary embolism be prevented or its incidence reduced. Good results from prophylactic heparin in selected cases have been recorded and this, combined with early exercises and massage to improve the venous circulation, may form the basis of even better results in the future.

### DISCUSSION

*Mr Graham* opened the discussion by proposing a vote of thanks to the speakers for their presentation of an important subject. The facts referred to showed how much we owed to the work done by the physiologists, and emphasised the importance of the basic sciences for those who intended to specialise in medicine and in surgery.

While the use of anticoagulants such as heparin would prove of help in vascular surgery, their chief value would be in the prevention and treatment of thrombosis occurring after operation and in the puerperium. *Mr Graham* had gained the impression from the speakers that the results were encouraging, and it was clear that a valuable addition had been made to our means of therapy in relation to this serious complication. It was apparent that a patient with signs of thrombosis in the leg, possibly extending to the deep veins, could expect relief of symptoms after two or three days treatment with heparin, and that it was safe to allow the patient up a few days later. After anticoagulant treatment the thrombosis showed no further tendency to spread, and convalescence was greatly shortened. *Mr Graham* asked if *Professor Learmonth* could explain how it was that there was little or no tendency to separation of the clot and pulmonary embolism after the treatment with heparin had been instituted. He had been impressed by the results in some of *Professor Learmonth's* cases, and by the care with which *Miss Burt* had made and recorded her observations.

*Mr Jeffrey* said that he had been much impressed by those cases he had seen treated by heparin. It was most desirable, where a thrombosis had developed, to keep it to the lower leg in order to give the patient a decent chance of recovery. If it spreads to the thigh the chances of return to a normal limb are poor, though the outlook is probably better now with heparin.

*Mr Jeffrey* was interested in *Dr Matthew's* cases in which pulmonary emboli developed in two cases of deep thrombosis which had heparin therapy.

Was this due to inadequate dosage; or was it due to liquification of the clot by heparin? He had heard of a case recently in which the surgeon had been called in to see a case of white leg occurring after puerperium. She was started on full doses of heparin, but developed a fatal pulmonary embolism twenty-four hours thereafter.

*Dr Fahmy* asked Miss Burt whether she had investigated the possible effect of heparin on the breast-fed baby of a mother treated by this therapy. The matter had been investigated in America, where it was shown that bleeding and clotting times in the babies showed prolongation of both, or only in clotting time, in more than one-third of the cases. It would appear to be of value to the obstetrician to know whether babies did or did not suffer any deleterious effect from the therapy given to the mother.

*Sir Henry Wade* said that there was not one practising surgeon present who had not experienced the tragedy of pulmonary embolus. The case progresses normally and satisfactorily and is getting up, perhaps going home in a day or two, when quite suddenly and unexpectedly death occurs.

He was anxious to know the possibilities of prophylactic treatment in these cases. Is the general surgeon to give it as a routine treatment? In the Mayo Clinic 1000 cases had been treated by the administration of thyroid, but he could not recall whether the result was wholly satisfactory.

*Dr Robertson* asked if there was any justification for using anticoagulants in the two forms of thrombosis met with most frequently in general practice; namely, cerebral thrombosis and coronary thrombosis.

*Dr John Gillies* was interested to know if the giving of anticoagulants was justified in cases such as fracture of neck of femur, particularly as a possible preventive of pulmonary embolism occurring at the time of reduction.

*Dr Sinclair* said he had no recollection of fatality ascribed to thrombosis occurring after cataract extraction. He had, however, experience of patients dying from pneumonia following influenza contracted during the period of recovery after that operation.

Perhaps the fact that his patients were always maintained in a reclining position (not flat) while in bed after extraction of cataract, may have helped to prevent thrombosis in the femoral vein by flexure of the hip. This position certainly proved advantageous in general comfort.

*Mr J. R. Cameron* brought up the question of ligation therapy, at present the alternative treatment of thrombosis. He wondered as to the indications for a combination of ligation with anticoagulants. Such a case, he felt, should be dealt with on its own merits. A difficulty in ligation was deciding the occasion and site and in anticoagulants estimating the quantity.

*The President* referred to the question of prophylaxis of thrombo-phlebitis. Unfortunately this horrible condition spreads beyond the realm of general surgery. In cataract operations one is accustomed to assure the patient that, whatever may happen, there is no danger to life. Then perhaps about the tenth day when everything seems to be going all right the patient sits up in bed and falls back dead. Should prophylactic treatment be instituted for all such cases?

*Professor Learmonth*, replying to Mr Graham's question as to why the clot which is already there does not spread after heparin therapy, stated that ideally the aim in giving heparin was to prevent the clot from reaching a large vein. The terminal part of the thrombus was always that which gave rise to an embolus, and that did not occur so long as the clot was confined to small veins such as those in the muscles of the calf of the leg.

Professor Learmonth was somewhat disturbed by Mr Jeffrey's gloomy view with regard to patients with "white leg"—that the leg remained permanently swollen. This was not the case; "white leg" might be treated with benefit after variable intervals—as long as four years.

He considered the question of the possibility of prophylactic treatment an important one in ordinary surgical work. Slowness of circulation was one cause of thrombosis, for which a great deal had been accomplished by routine exercises supervised in the wards to the accompaniment of a rickety gramophone by the competent young women from the Physiotherapy Department. At the other extreme there was the surgeon who got his patient up the day after operation. This was not a new type of therapy; it did not banish the occurrence of thrombosis but reduced the incidence. Professor Learmonth thought that from the sixth day the patient should be watched for signs of thrombosis.

Regarding the difference between ligation and anticoagulants, it was quite easy to stop the process in superficial veins by bandaging the leg above the level of the thrombosis and allowing the patient to walk about. There were as many as 35 recorded cases now of ligation of the superior vena cava with no detrimental effect to the patient if below the level of the renal veins.

*Dr Richards*, replying to the question about cerebral and coronary thrombosis, said that anticoagulants might not be useful in regard to the initial attack, but might be used to prevent further thrombosis and lessen the dangers from the formation of a mural thrombus.

# BLOOD CHANGES IN THE AGED

## PART II

By OSCAR OLBRICH, M.D., Ph.D., F.R.C.P.E.\*

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(Continued from p. 321)

### FRAGILITY

THE behaviour of erythrocytes in media hypotonic with respect to blood plasma has been the subject of very many investigations. Many techniques have been devised for studying this behaviour, and many attempts have been made to find a satisfactory quantitative expression for the "osmotic resistance" or "fragility" of the red cells.

Fundamentally, all methods consist in suspending the red cells in a relatively large volume of medium (generally sodium chloride solution), using a series of such media of known composition, and observing in each case the proportion of the cells which undergo hæmolysis. Measurement may be approximate by visual examination only; it may be somewhat more accurate by actual count of the surviving cells; or it may be by colorimetric determination of the released hæmoglobin. The result may be expressed in terms of the range of sodium chloride concentration over which hæmolysis occurs, or in terms of the concentration of sodium chloride which causes hæmolysis of some more or less arbitrarily chosen proportion of the cells.

The position is so unsatisfactory that we have been led to investigate the problem of the determination of the osmotic fragility of the red cells. The validity of the method and the results we have obtained will be discussed elsewhere; here we merely outline the technique we have adopted and consider the results only in their bearing on the differences between the cells of aged persons and those of the young.

### TECHNIQUE

The sodium chloride solutions had the following concentrations, chosen because experience showed them to cover adequately the range over which hæmolysis occurred:—

0.500 0.485 0.470 0.455 0.440 0.425 0.410 0.380  
0.350 0.290 and Distilled Water

To 9.5 ml. of each solution was added 0.5 ml. of venous blood with Win-trobe's mixture as anticoagulant, and the mixture was thoroughly but gently agitated. A mixture of 0.5 ml. of blood and 9.5 ml. of distilled water was similarly prepared and taken as representing complete hæmolysis. The tubes were centrifuged after standing for five hours. The colour of the clear supernatant fluid in each tube was determined by means of the Spekter photometer using a green filter (wavelength 604 microns).

\* Aided by a grant from the Medical Research Council.

Taking the value of the distilled water-blood mixture as 100, the percentage hæmolysis was calculated for each blood-saline mixture. The percentage hæmolysis throughout the series, plotted against the corresponding sodium chloride concentrations, gave a sigmoid curve, as shown in Fig. 3.

Tables X and XI show the average percentage of cells hæmolysed at the various sodium chloride concentrations for 77 persons over 54 years of age and for 38 young persons between the ages of 17 and 38. Cursory examination of this table shows that in the aged group hæmolysis occurs at an appreciably higher sodium chloride concentration than in the younger group; that there is, for any given

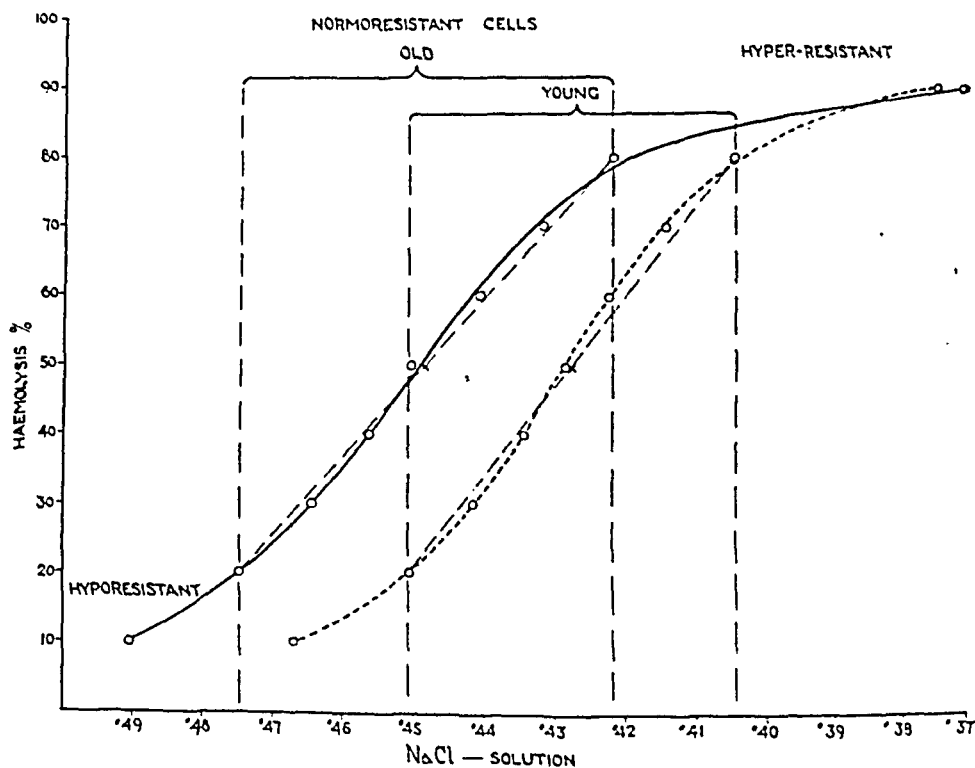


FIG. 3.—Percentage hæmolysis plotted against sodium chloride solution as base. Sigmoid shaped curve = integrated frequency distribution.

concentration of sodium chloride above 0.38 per cent., greater cell hæmolysis in the blood of the aged than the young. Further examination showed that, in both groups, there is a slightly greater percentage of red cells hæmolysed, at each salt concentration, in the blood of males than of females.

To examine the significance of these findings Table XII was constructed. It shows the concentration of sodium chloride at which various percentages of the cells underwent hæmolysis, the figures being obtained from graphs of the type illustrated in Fig. 3. For each level of hæmolysis chosen, the range of sodium chloride concentration was determined and the mean value. Calculation gave the standard deviation and the coefficient of variation. Inspection of these figures

# BLOOD CHANGES IN THE AGED

shows that both the age and sex differences mentioned above are statistically significant. It also shows that the fragility of the red cell population in the old subjects is more variable than in the young. This is shown more clearly by calculating the mean value of the coefficients of variation in the two groups, and computing the coefficients of variation of these means. It is evident, however, that this is mainly due to the very high coefficients of variation in the aged group at

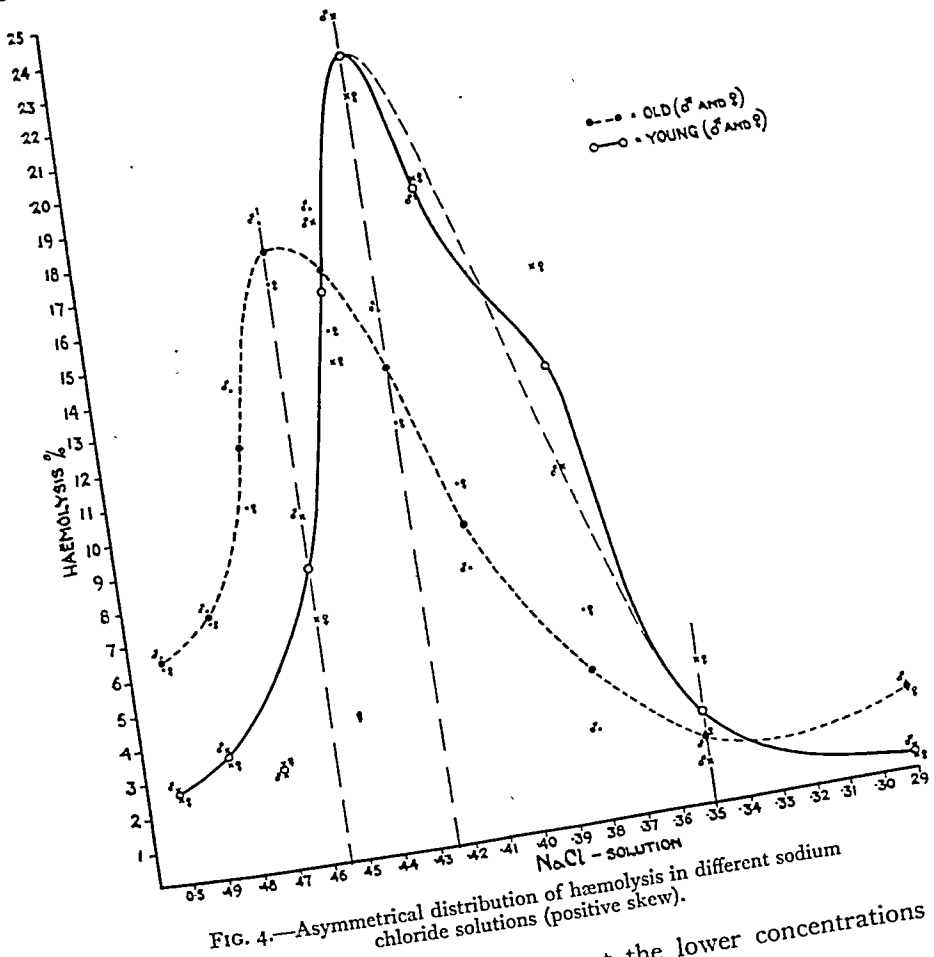


FIG. 4.—Asymmetrical distribution of haemolysis in different sodium chloride solutions (positive skew).

higher percentages of haemolysis (*i.e.* at the lower concentrations of sodium chloride).

In seeking for an explanation of the differences between the red cells of aged persons and those of the young, it has to be remembered that the red cells of the blood do not form a homogeneous population. They vary, for instance, in age. The sigmoid form of the curve relating to percentage of cells haemolysed to sodium chloride concentration suggests that three ill-defined groups of cells may be distinguished. The main group of "normo-resistant" cells haemolysed



## RESULTS

TABLE X

*Young—Males and Females*

NaCl per cent.	Percentage of Red Cells Range.	Hæmolysed Mean.	No. of Cases.	Standard Deviation.	C.V.	S.E.
0.50	0.0-7.5	2.65	38	1.86	70.2	±0.302
0.485	0.4-13.3	6.15	36	3.32	53.98	±0.553
0.47	1.7-21.7	9.1	37	4.89	53.73	±0.804
0.455	2.6-34.2	17.7	36	8.42	47.6	±1.40
0.44	6.1-61.7	34.15	38	13.7	40.1	±2.22
0.425	13.8-78.3	57.3	38	16.73	29.2	±2.72
0.41	23.1-89.6	76.35	38	14.7	19.25	±2.38
0.38	57.7-98.3	89.7	38	6.32	7.05	±1.025
0.35	85.3-98.3	92.4	37	2.54	2.75	±0.42
0.29	85.3-98.3	93.0	38	2.44	2.62	±0.396

*Old—Males and Females*

NaCl per cent.	Percentage of Red Cells Range.	Hæmolysed Mean.	No. of Cases.	Standard Deviation.	C.V.	S.E.
0.50	0.0-19.2	6.45	75	4.58	71.0	±0.53
0.485	0.0-34.2	14.05	77	7.42	52.81	±0.85
0.47	3.8-54.5	26.35	77	12.65	48.1	±1.44
0.455	9.6-75.4	44.15	77	17.06	38.6	±1.95
0.44	15.7-93.6	61.25	77	17.83	29.0	±2.03
0.425	32.2-93.6	75.3	77	13.86	19.7	±1.58
0.41	41.0-95.4	84.45	77	9.59	11.35	±1.09
0.38	56.2-98.4	88.9	77	6.63	7.45	±0.75
0.35	72.4-98.4	90.85	77	4.9	5.39	±0.56
0.29	84.0-99.2	93.3	77	3.16	3.39	±0.36

TABLE XI

*NaCl Solutions*

No. of Observations.	Sex.	Age.	Average Age.	0.50	0.485	0.47	0.455	0.44	0.425	0.41	0.38	0.35	0.29
<b>OLD</b>													
35	Male . . .	55-86	75.3	6.6	14.4	28.4	47.1	66.0	78.4	86.3	89.0	91.0	93.5
42	Female . . .	54-95	77.0	6.3	13.7	24.3	41.2	56.5	72.2	82.6	88.8	90.7	93.1
77	Male and female	54-95	76.2	6.45	14.05	26.35	44.15	61.25	75.3	84.45	88.9	90.85	93.3
<b>YOUNG</b>													
15	Male . . .	14-38	24.8	2.8	6.5	9.3	19.4	37.9	62.2	81.0	91.4	92.6	93.3
23	Female . . .	17-36	26.3	2.5	5.8	8.9	16.0	30.4	52.4	71.7	88.0	92.2	92.7
38	Male and female	14-38	25.6	2.65	6.15	9.1	17.7	34.15	57.3	76.35	89.7	92.4	93.0

This table shows the mean values of the per cent. hæmolysis observed for different salt solutions in 77 old subjects and in 38 young of both sexes.

TABLE XII

*Fragility of the Blood Cells in the Old—Male and Female*  
77 Cases

Percentage Hæmolysis.	Range.	Mean.	Standard Error = S.E.	Standard Deviation = $\sigma$ .	Coefficient of Valuation in per cent.
10	0.5700-0.4540	0.4905	0.00143	0.0125	2.55
20	0.4970-0.4360	0.4748	0.00153	0.0134	2.822
30	0.4890-0.4330	0.4645	0.00149	0.0131	2.820
40	0.4790-0.4130	0.4563	0.00158	0.0139	3.05
50	0.4730-0.3920	0.4509	0.00171	0.015	3.33
60	0.4660-0.3730	0.4412	0.00180	0.0158	3.58
70	0.4590-0.3550	0.4319	0.00205	0.018	4.17
80	0.4490-0.3250	0.4170	0.00285	0.025	5.99
90	0.4430-0.2880	0.3706	0.00525	0.046	12.41
100	...	D.W.	...	...	...

Mean of C.V. = 4.525

$\sigma$  of C.V. = 9.4419

C.V. of C.V. = 208 per cent.

*Fragility of the Blood Cells in the Young—Male and Female*  
38 Cases

Percentage Hæmolysis.	Range.	Mean.	Standard Error = S.E.	Standard Deviation = $\sigma$ .	Coefficient of Variation in per cent.
10	0.4940-0.4330	0.4672	0.00259	0.016	3.42
20	0.4730-0.4170	0.4509	0.00211	0.013	2.88
30	0.4600-0.4040	0.4417	0.00195	0.012	2.72
40	0.4520-0.3950	0.4347	0.00195	0.012	2.76
50	0.4470-0.3870	0.4286	0.00195	0.012	2.80
60	0.4410-0.3780	0.4226	0.00162	0.010	2.37
70	0.4330-0.3670	0.4154	0.00179	0.011	2.65
80	0.4260-0.3560	0.4048	0.00227	0.014	3.46
90	0.4060-0.2880	0.3745	0.00389	0.024	6.41
100	...	D.W.	...	...	...

Mean of C.V. = 3.22

$\sigma$  of C.V. = 3.50

C.V. of C.V. = 108 per cent.

The above two tables were constructed by plotting every individual's fragility curve on squared paper and reading off the salt solution corresponding to different levels of hæmolysis; the results were then grouped according to age and sex, and averaged for each level of hæmolysis. The standard deviation and the coefficient of variation of the red cell fragility are also given for each level of hæmolysis. Below each table is shown the mean value, standard deviation and coefficient of variation of the coefficients of variation for the old group, and similarly for the young. Comparison of these two mean values shows that the fragility is on the whole more variable for the old than for the young—indeed it is more variable at every hæmolysis level above 30 per cent. Comparison of the coefficients of variation shows that this variability in itself varies more widely at the different levels of hæmolysis for the old than for the young, this being mainly due to the high variability of the hyper-resistant cells in the old.

over a rather narrow range of salt concentration and is represented by the central, almost straight, section of the curve. Hæmolysed over a wider range of higher salt concentrations are the "hypo-resistant" cells. Hæmolysed only when the salt concentration is lower than is necessary for the normo-resistant cells are the "hyper-resistant" cells.

That some such division into groups is real is suggested when the figures of Table XI are plotted on probability paper (Fig. 5), a procedure which was suggested by Professor Gaddum. The abscissæ represent

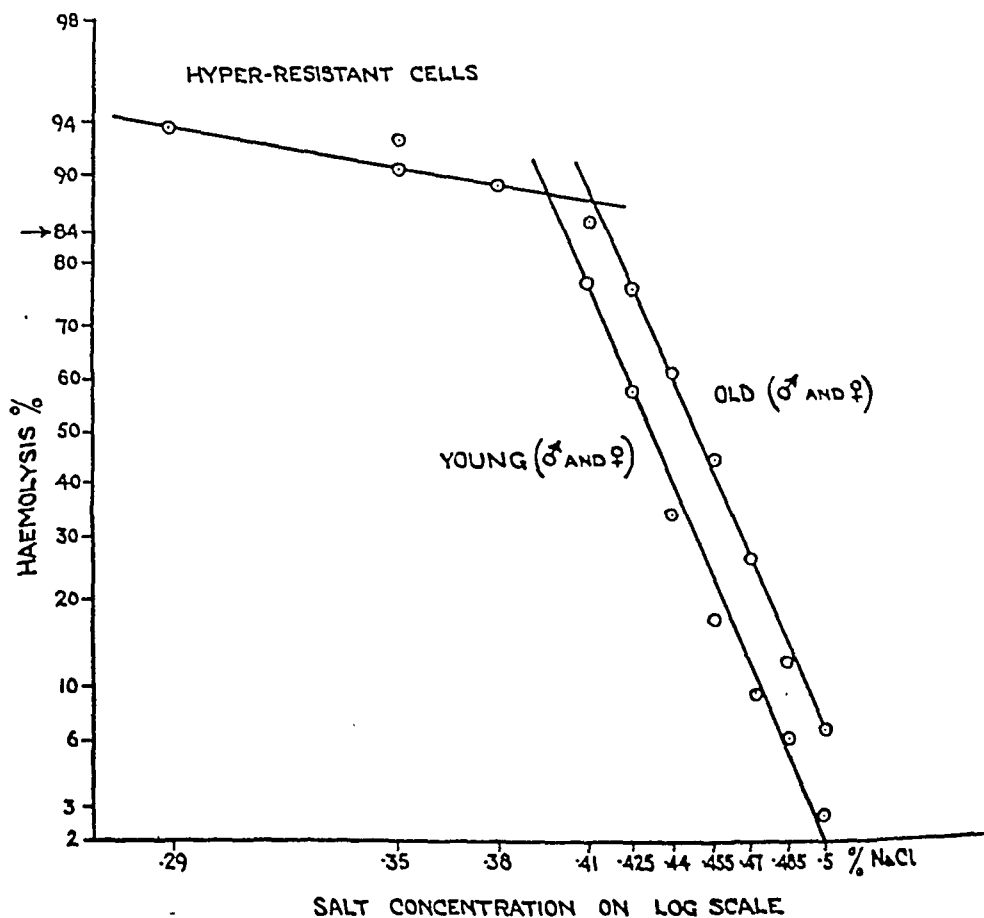


FIG. 5.—Percentage haemolysis plotted on probability paper with salt concentration on logarithm scale.

sodium chloride concentrations, the ordinates represent mean percentage hæmolysis on a probability scale such that distances are proportional to the corresponding areas under the Gaussian normal curve. The plotted points for the old persons (Fig. 4, continuous line) fall along two distinct straight lines, cutting at about the 84 per cent. level of hæmolysis. This strongly suggests the existence of the two groups in the red cell population which we have named normo-resistant and hyper-resistant. For the group of young persons (broken line), the result is similar though less precise. The figures are not, however, sufficiently full to show clearly the existence of the third hypo-resistant group.

By plotting hæmolysis on probability paper, with a logarithmic base for the salt concentration, approximately straight parallel lines are obtained up to the 84 per cent. level of hæmolysis in old and young. A population of red cells whose resistance to hæmolysis was normally distributed would be represented by one straight line in the figure; the broken line obtained suggests the presence of a heterogenous population consisting of normo- and hyper-resistant cells, each component being approximately normally distributed, this statement applying to both old and young people (Fig. 5).

On the basis of this division of the red cell population into three groups, the fragility differences between the red cells of the aged and those of the young could be described as indicating a markedly greater number of hypo-resistant cells in the blood of the aged, and some increase also in the number of the hyper-resistant cells. Apart from this, however, age would appear to be accompanied by some increase in the fragility of the main group of normo-resistant cells.

It is tempting to correlate the osmotic resistance of the individual erythrocyte with its age. Unfortunately it is not at present possible to determine the age of an erythrocyte except in the case of reticulocytes. It has been reported that reticulocytes have a lower osmotic resistance (*i.e.* are hæmolysed at higher salt concentrations) than mature erythrocytes, and this might be held to suggest a general increase of osmotic resistance with increasing cell age. The data for reticulocytes have, however, been obtained in cases with some kind of blood disorder, in which, therefore, the reticulocytes were actually abnormal (Mermod, Duck, 1935).

The same objection may equally be raised against data suggesting the opposite conclusion—that osmotic resistance decreases with increasing age of the cell. Such data are supplied by Reicher (1921) and Simmel (1923), who found decreased osmotic resistance in aplastic anæmia where the marrow function is impaired, and by Daland and Zetzel, who found increased osmotic resistance coinciding with increased bone-marrow activity in secondary post-hæmorrhagic anæmia. Evidently the temptation is one to be resisted, at least until much more evidence has been obtained.

The normal environment of the red cell may affect its fragility, as has been shown (Ottiker, 1914, and later others) in experiments involving saturation of the blood with carbon dioxide. Such treatment decreases the osmotic resistance of the cells and it is just possible that some such factor might account, at least in part, for the differences we have observed between the cells of aged and young persons. When, however, cells from aged persons were separated from their plasma by centrifuging and were re-suspended in plasma from young persons, the "fragility curve" was unaltered and remained typical of aged persons. Conversely, cells from young persons, suspended in plasma from old persons, have unchanged fragility. The osmotic resistance

of the cell then, in so far as it is affected by age, is a property of the cell itself.

References in the literature to the osmotic behaviour of the red cells of the aged are very scanty. Reicher (1921) found a decreased osmotic resistance, such as was shown by our own data, whereas Baliff and Marza (1923) found no difference between the cells of aged persons and those of the young. We believe that our own data are sufficiently reliable to establish the existence of the changes we have described in the osmotic resistance of the red cells with advancing years. Although the explanation is still obscure, we regard as of equal importance the general change in osmotic resistance and the greater variability with its suggestion of altered proportions of hypo-, normo- and hyper-resistant cells.

*(To be continued)*

## NOTES

At the Annual Meeting of the College held on 4th December 1947, Dr W. D. D. Small, C.B.E., was elected President, and Drs R. Cranston Low, L. S. P. Davidson, J. D. S. Cameron, C.B.E., H. L. Wallace, I. G. W. Hill, C.B.E., and Sir David K. Henderson were elected to form the Council for the ensuing year.

Sir David K. Henderson was nominated Vice-President.

Drs R. Cranston Low and A. Ninian Bruce were elected Representatives of the College on the Board of Managers of The Royal Infirmary of Edinburgh for the ensuing year.

At a meeting of the Royal College of Surgeons of Edinburgh, held on 17th December 1947, Mr Frank E. Jardine, President, in the Chair, the following who passed the requisite examinations were admitted Fellows:—Melville George Allen-Mersh, M.S., M.F. BENGAL MED. COLL. 1936, L.R.C.S.E. 1947;

Nosrat Ameli, M.B., CH.B. UNIV. BIRM. 1937; George Stevenson Anderson, M.B., CH.B. UNIV. ABER. 1938; Una Aranha, M.B., B.S. UNIV. BOMBAY 1941, M.D. UNIV. BOMBAY 1945; Abraham Jacobus Stephanus Burger, M.B., CH.B. UNIV. CAPE TOWN 1931; Bernard Zalman Claman, M.D. UNIV. MANITOBA 1944; Thomas Richard Brian Courtney, M.B., B.S. UNIV. MELBOURNE 1935; Robert D. Cowan, M.D., WESTERN UNIV. ONTARIO 1942; Thomas Tibbott Davies, M.R.C.S.ENG., L.R.C.P.LOND. 1938; Arthur Leonard Deacon, M.B., CH.B. UNIV. BIRMINGHAM 1935; John Lindsay Douglas, M.B., CH.B. UNIV. GLASGOW 1939; William Drummond, M.B., CH.B. UNIV. EDIN. 1936; Geoffrey Eric Dunkerley, M.B., B.S. UNIV. LOND. 1933; John Rawson Elder, M.B., CH.B. UNIV. NEW ZEALAND 1932; Charles Dale Falconer, M.B., CH.B. UNIV. EDIN. 1939; William Douglas Giffen, M.B., CH.B. UNIV. EDIN. 1938; James Stephen Glennie, M.B., CH.B. UNIV. ABERDEEN 1940; John Telfer Gray, M.B., CH.B. UNIV. EDIN. 1945; Lawrence Mitchell Greene, M.D. UNIV. TORONTO 1937, L.M.C. CANADA; George Inglis Henderson, M.B., CH.B. UNIV. ST ANDREWS 1927; Neil Geddes Clarkson Hendry, M.B., CH.B. UNIV. ABERDEEN 1939; Salomon Henson, M.B., CH.B. UNIV. LIVERPOOL 1938; Frank Geoffrey Hibbert, M.B., CH.B. UNIV. MANCHESTER 1937; Werner Paul Hirsch, M.R.C.S.ENG., L.R.C.P. LOND. 1940; John Rowland Hughes, M.B., CH.B. UNIV. LIVERPOOL 1940; Thomas Blythe Hutton, M.R.C.S.ENG., L.R.C.P. LOND. 1939; Harold Bell Jackson, M.D., C.M. UNIV. MCGILL 1943; Isaac Jacobson, M.B., CH.B. UNIV. CAPE TOWN 1935, M.R.C.S.ENG., L.R.C.P. LOND. 1936; John Jankowitz, M.B., B.CH. UNIV. WITWATERSRAND 1938; John Hugh Jordan, M.R.C.S.ENG., L.R.C.P. LOND. 1942; Peter Francis King, M.R.C.S.ENG., L.R.C.P. LOND. 1945; Richard George Rowley Langford, M.B., CH.B. UNIV. CAPE TOWN 1940; Matthew David Leitch, M.B., B.CH. UNIV. DUBLIN 1940; George Stephen Lester, M.B., CH.B. UNIV. BIRMINGHAM 1936; Arthur Morris Loughran, M.B., CH.B. UNIV. EDIN. 1939; Alec. Lurie, M.B., CH.B. UNIV. CAPE TOWN 1932; Wallace Arnold McAlpine, M.D. UNIV. MANITOBA 1944; John Nelson Wilson McCagie, L.R.C.P. AND S.EDIN. (TRIPLE) 1940; Vivian Vance McCusker, M.B., B.CH. UNIV. CAPE TOWN 1935; Archibald McDougall, M.B., CH.B. UNIV. GLASG. 1938; John Alan Macfarlane, M.B., CH.B. UNIV. EDIN.

1941; James Gordon McFetridge, M.D. UNIV. MANITOBA 1937; Kenneth MacIver MacKenzie, M.B., CH.B. UNIV. GLASGOW 1937; George Campbell McKinlay, M.B., CH.B. UNIV. GLASGOW 1939; Louis Anselm Halsey McShine, M.R.C.S.ENG., L.R.C.P. LOND. 1939; William Albert Watt Maney, L.R.C.P. AND S.EDIN. (TRIPLE) 1939; Maxwell Julius Maxwell, M.B., CH.B. UNIV. LEEDS 1927; Leopold Mirkin, M.B., CH.B. UNIV. CAPE TOWN 1939; William Murdie, M.B., CH.B. UNIV. EDIN. 1943; David Sinclair Murray, M.B., CH.B. UNIV. EDIN. 1940; James Fulton Neil, M.R.C.S.ENG., L.R.C.P. LOND. 1942; Maurice Wingate Paterson, M.B., CH.B. UNIV. EDIN. 1937; Richard Hugh Purnell, M.R.C.S.ENG., L.R.C.P. LOND. 1934; Balasubramaniam Ramamurthi, M.B., B.S. UNIV. MADRAS 1943; Jacob Israel Rossman, M.D. UNIV. TORONTO 1939; John Edward Rowlands, M.R.C.S.ENG., L.R.C.P. LOND. 1933; Max Phillip Shapiro, M.R.C.S.ENG., L.R.C.P. LOND. 1939; Eric George Fergusson Shaw, M.R.C.S.ENG., L.R.C.P. LOND. 1942; Rae Henderson Simpson, M.B., CH.B. UNIV. GLASGOW 1939; Samuel Ronald Sinclair, M.B., B.CH., B.A.O. QUEEN'S UNIV. BELFAST 1936; Mohindar Singh Sindhu, M.B., B.S. UNIV. PUNJAB 1934; Thomas Sinclair Stewart, M.B., CH.B. UNIV. MANCHESTER 1939; Cuthbert Ridley Strother-Stewart, M.B., CH.B. UNIV. EDIN. 1943; Stuart Douglas Stock, M.R.C.S.ENG., L.R.C.P. LOND. 1941; Ivan Samson Durham Thomson, M.B. CH.B. UNIV. EDIN. 1940; John Dunlop Thomson, M.B., CH.B. UNIV. GLASGOW 1939; Ahmed Khan Toufeeq, M.B., B.CH. UNIV. WALES 1943; William Arthur Leigh Tucker, L.R.C.P. AND S.EDIN. (TRIPLE) 1938; Harold Preston Watson, M.B., CH.B. UNIV. ST ANDREWS 1938; Arthur Low Webster, M.B., CH.B. UNIV. ST ANDREWS 1943; Thomas Barrett Whiston, M.B., CH.B. UNIV. EDIN. 1943; George William Wigg, M.R.C.S.ENG., L.R.C.P. LOND. 1924; Harry William George Williams, M.R.C.S.ENG., L.R.C.P. LOND. 1939; Hugh Osborne Williams, M.B., CH.B. UNIV. LIVERPOOL 1942; Joseph Edgar Wilson, M.B., B.S. UNIV. DURHAM 1930; Henry Cook Worrall, M.B., CH.B. UNIV. EDIN. 1941; Margaret Patricia Yeoman, M.B., CH.B. UNIV. EDIN. 1942; Graeme Bruce Young, M.B., CH.B. UNIV. EDIN. 1939; Ian Strang Young, M.B., CH.B. UNIV. GLASGOW 1942; Harold Zalin, M.B., CH.B. UNIV. LIVERPOOL 1937.

*Higher Dental Diplomates.*—The following candidates having passed the requisite examinations were admitted Higher Dental Diplomates—John Richard Vivian Buckley Gibson, L.D.S., R.C.S.ENG. 1944; John George Alexander Piper, L.D.S., R.C.S.EDIN. 1942; Isaac Stein, L.D.S., R.C.S.EDIN. 1926; M.D.S.(HONS.) WITWATERSRAND 1946.

At a Graduation Ceremonial held in the Upper Library on Friday, 19th December 1947, the following degrees were conferred:—

University of  
Edinburgh

*The Degree of Doctor of Medicine:*—Tariq Munir Abbas, Iraq, M.B., CH.B. 1943; Arthur Whitley Branwood, England, M.B., CH.B. 1942 (*Commended for Thesis*); Frederick Smith Fiddes, O.B.E., Scotland, M.B., CH.B. 1931; Scott Lawson Forrest, Scotland, M.B., CH.B. 1934; James Alan Longmore Gilbert, Canada, M.B., CH.B. 1941 (*Highly Commended for Thesis*); James Wright Rae, Scotland, M.B., CH.B. 1936; Syed Abdur Rahman, India, M.B., CH.B. 1926.

*The Degree of Doctor of Philosophy—In the Faculty of Medicine:*—Mohamed Lutfi Bayoumi, M.B., B.CH.(FOUAD).

*The Degrees of Bachelor of Medicine and Bachelor of Surgery:*—Alexander McDonald Allan, Scotland; Henry Waters Bisset, Scotland; George Brown,

Scotland; Margaret Whatley Brown, Scotland; Jean Buchanan, Scotland; Frederick Gordon Cumming, Scotland; Iain Hamish Padraig Doherty, Scotland; Thomas Horne Donaldson, Scotland; Leslie Albert Gess, England; Robert Reid Gillies, Scotland; Adair Girby, Egypt; George Taylor Graham, Scotland; Janet Hazell, England; Lewis Johnston Murray Jamieson, Scotland; Herbert Arnold Jones, Scotland; Hugh Mackie Kirkpatrick, Scotland; Frederick Ernest Kohler, Scotland; Robert Graham Krause, Scotland; Marjorie Violet Kydd, Scotland; Anne Marjory McCartney, Scotland; Brian Tomas Mulligan, Scotland; Alastair Morrison Nelson, Scotland; William Henry Nisbet, Scotland; Susan Barbara Gyan-koramah Ofori-Atta, Gold Coast; James Gordon Parish, England; Alexander Geoffrey Bruce Poole, Scotland; Alasdair Diarmid Ross, Scotland; Jean Ruth Williamina Ross, B.Sc., Scotland; Kenneth Saltman, Wales; Desmond Allen Smith, Eire; Brian James Sproule, England; Diana Stewart, England; Leila Margaret Wojtczak (*née* Sinha), India; Lesley Leigh Dick Wood, Scotland.

*The Polish School of Medicine—The Degrees of Bachelor of Medicine and Bachelor of Surgery*.—Jerzy Arendt, Stanislaw Goldberg (*in absentia*), Regina Goldstein (*in absentia*), Zbigniew Golen (*in absentia*), Józef Lomaz, Wanda Piłsudska (*in absentia*), Henryk Podlewski, Stanislaw Pogonowski, Wiktor Rosenberg (*in absentia*), Emanuel Wilder (*in absentia*), Mieczyslaw Wojciechowski.

THE examinations of the Board of the Royal College of Physicians of Edinburgh, the Royal College of Surgeons of Edinburgh, and the Triple Qualification Board Royal Faculty of Physicians and Surgeons of Glasgow, have just concluded at Edinburgh. The following passed the Final Examinations, and were granted the diploma of L.R.C.P. EDIN., L.R.C.S. EDIN., L.R.F.P. AND S. GLASGOW:—Afolabi Alakija, James Morris Brownlie, Leo Charles, William James Charles Colin-Thome, Ronald Skae Cowie, Aziz Mohamed Darwish, Thomas Peacock Edwards, Peter Hin Tak Fok, Sidney Gordon, John Alexander Gray, William Sidney Hall, Maurice Harris, Patricia Eve Hartley, John Mackintosh Hillock, Emanuel Katz, Douglas Park Keith, Stanley Lipson, Michael Lloyd-Jones, Peter Macpherson, Hilary Ethel Clara Millar, Henry Gordon Clement Payne, Alfred Ian Richardson, James Railton Scott, Joan Cuthbert Rutherford Shiell, Harry Simmons, Hamish Stuart Sloane, John David Stewart.

## NEW BOOKS

*Health and Social Welfare*, 1947. Advisory Editor, Lord HORDER, M.D., B.Sc., F.R.C.P. Pp. 527. London: Todd Publishing Company. 1947. Price 25s. net.

This annual reference work claims to be an authoritative and invaluable guide and companion for those interested in any or all of the many facets of health and social welfare. It certainly contains a vast amount of information. There are official directories of various public departments, official statements of the activities of these, and unofficial accounts of societies and institutions and many other features of similar character.

In addition there are a few articles on subjects of general interest, and one on careers in health and social welfare.

A section on "Who's Who" is not comprehensive enough to be really valuable and is open to certain obvious objections.



*The Development of Inhalation Anaesthesia.* By BARBARA M. DUNCUM, D.PHIL. (OXON). Pp. xvi+640, with 161 illustrations. London: Oxford University Press. 1947. Price 35s.

History can be as dry as dust, but so far as the discovery of anaesthesia is concerned, it has been coloured by dramatic incidents and enriched by great personalities. In the past, books dealing with this subject have tended to exaggerate the melodrama and have suffered in value on account of saccharose sentiment. Dr Duncum has avoided such pitfalls and has presented a straightforward, well-documented record of the discovery of inhalation anaesthesia and its subsequent evolution. She deals particularly with the period 1846-1900 but with appropriate comment on the pre-anaesthetic period and on more recent developments. Interest in the subject is well sustained throughout by skilful leavening of the historical and scientific data by biographical detail. Much painstaking research must have been undertaken in collecting the material for this work, which seems undoubtedly destined to be the standard book on this special aspect of medical history. The many illustrations are excellent, the format is clear and the whole production has a finesse which is welcome after the austerity of wartime books.

*Bacteria in Relation to Domestic Science.* By C. E. DUKES, M.D., M.SC., D.P.H. Pp. 240, with 9 illustrations. London: Oxford University Press. 1947. Price 12s. 6d. net.

This book was written mainly for students of domestic science and household and social science. Its range covers the elements of the bacteriology of air, soil, water and beverages, the preservation of food in a practical way, and the various forms of food poisoning in considerable detail.

The book is written in a pleasant and easily read style, and narrates many episodes, such as those of "Typhoid Mary" and of the German food inspector who died of Gaertner food poisoning in attempting to prove that some sausage meat was edible, which help to fix facts in the student's mind.

It goes considerably beyond what might be thought necessary for students of domestic science, and students and practitioners of medicine also will find it a useful and practical handbook.

*Geriatrics.* Published bi-monthly by American Geriatrics Society under the Editorship of A. E. HEDBACK, M.D. Minneapolis. Price \$4.00 a year.

With the continued advances of medical science, more people are surviving to older ages and the number of old people in the community is steadily rising. The medical care of these people is therefore becoming of increasing importance. In order to discuss the problems involved and disseminate knowledge about the care of the aged and the ageing, the American Geriatrics Society founded this new journal a year ago. It carries informative articles on all aspects of the problem and should be welcomed by all who have the care of old people.

*Excerpta Medica.* Section XIII. Dermatology and Venerology. Under the general editorship of M. W. WOERDEMAN, M.D., F.R.N.A.S.

We have received a copy of the publication of a new abstracting service. The scheme is to provide each month a complete series of abstracts of world medical literature arranged in 15 separate sections. It is hoped to issue informative summaries which will condense the essential information and so save the time of readers who cannot cover the whole field for themselves and, since new discoveries so rapidly pass out of date, to publish the abstracts with as little delay as possible.

In the copy before us the abstracts are all in English. They vary considerably in length, some being quite short, others giving considerable detail. They are well written and informative and should prove of the greatest service to busy medical men. We wish the new venture the success that it deserves.

## NEW EDITIONS

*Cushny's Pharmacology and Therapeutics.* By GROLLMANN and SLAUGHTER. Thirteenth Edition. Pp. 868, with 74 illustrations. London: J. & A. Churchill Ltd. Price 45s.

At the end of the last century Cushny first published his book on Pharmacology and Therapeutics, and gave to the medical profession a standard work to guide his colleagues along the lines of rational therapy. That his labour, and that of the authors of the book after he ceased to write, has been appreciated is indicated by the fact that the present edition is the thirteenth to appear. The advances made in pharmacology and therapeutics of recent years have been such that to have included them all in detail would have resulted in a volume of unwieldy size. The present authors are to be commended on the skill with which they have retained what was useful of the old edition, added, in sufficient detail for clarity, the established recent advances, and covered adequately the very recent drugs such as folic acid, BAL, streptomycin, curare, etc., indicating the lines along which progress may be anticipated. Though other works on the same subject, some of them very good, have appeared since Cushny first published his book, the present edition will ensure that the popularity that it has enjoyed in the past will be retained.

*Ellis's Anatomy.* Revised and edited by J. A. KEEN, M.B., F.R.C.S. Thirteenth Edition. Pp. xv+487, with 216 illustrations. London: John Murray. 1946. Price 42s. net.

Pauchet wrote about his *Pocket Atlas of Anatomy*, "It carries in it the germ of success—convenience." The same asset pertains to the latest edition of *Ellis's Anatomy* which is some 300 pages shorter than the tenth edition of 1887.

This book is an excellent short manual of dissection and regional anatomy. Lucid dissection instructions are given, with no words wasted. The illustrations are the same as in the last edition, with minor adjustments; though in some the lettering is not so clear as formerly, many have been improved with the addition of colour. A book to be thoroughly recommended.

*Student's Handbook of Surgical Operations.* By Sir FREDERICK TREVES. Eighth Edition, revised by CECIL P. G. WAKELEY, C.B., F.R.C.S. Pp. xi+574, with 281 illustrations. London: Cassell & Co. Ltd. 1946. Price 15s. net.

The eighth edition of this well-known little handbook has been extensively revised and much new matter added, particularly in the sections on neuro-surgery and thoracic surgery. In addition some fifty new illustrations have been incorporated.

For the most part the emphasis is still on the simpler anatomical procedures, as is right in a student's handbook, but there is also much practical detail for the post-graduate.

*A Handbook of Midwifery.* By Sir COMYNS BERKELEY. Thirteenth Edition. Pp. x+456, with 88 illustrations. London, Toronto, Melbourne and Sydney: Cassell & Co. Ltd. 1946. Price 12s. 6d.

The thirteenth edition of this well-known book written for pupil-midwives preparing for the examinations of the Central Midwives Board, as well as midwives and obstetric dressers, was revised by the author before his death although its publication was delayed till May 1947. The treatment of placenta prævia and the section on blood transfusion have been rewritten and brief mention made, sufficient for midwives' purposes, of the Rhesus factor. Otherwise it maintains its previous characteristics and for the most part gives a clear account of modern opinion and practice. In emergency situations very definite lines of action are described so that no confusion should result from indecision. It is interesting to note that in the treatment of both retained and adherent placenta the midwife is definitely advised to assist Credé's method of expulsion by first administering ergometrine. Will it stand the test of time?

*Eye Manifestations of Internal Diseases.* By I. S. TASSMAN, M.D. Second Edition. Pp. 614, with 243 illustrations. London: Henry Kimpton. 1946. Price 50s. net.

The first edition was published in 1942, and in so specialised a work the need already for a second edition is eloquent testimony to its usefulness among those for whom it is primarily designed, namely physicians and surgeons engaged in specialised practice. But an obvious appeal exists in the fact that here are to be found a large number of the rarer conditions in which eye manifestations are early presenting features in disease, many being beautifully illustrated.

The general physician must welcome the chance made so readily available of gaining an understanding of many problems about which his oculist colleague seeks his help. How true it is that many of the puzzling and intriguing medical cases enter hospital through the eye department. Professor Tassman deserves our grateful thanks for providing so valuable a reference.

*Diseases of Metabolism.* By GARFIELD G. DUNCAN, M.D., and 20 contributors. Second Edition. Pp. xviii+1045, with 167 illustrations and figures. London: W. B. Saunders Company. 1947. Price 60s. net.

Since its first appearance some five years ago this work has established itself as an authoritative source of information. During the past few years great advances have been made in many fields of metabolism and these are represented in the present issue. The book aims at offering the practitioner a practical basis for the understanding, diagnosis and treatment of the various metabolic disorders. Prominence is given to clinical considerations, but laboratory data have been included as aids in diagnosis and treatment. This excellent book should be in the hands of all practising physicians.

## BOOKS RECEIVED

- BROCKBANK, E. M., M.B.E., M.D. VICT., F.R.C.P. *The Conduct of Life Assurance Examinations.* Second Edition. (H. K. Lewis & Co. Ltd., London) 12s. 6d. net.
- Brompton Hospital Reports. Vol. XV. 1946. (Gale & Polden Ltd., Aldershot) 10s. net.
- FRANK, ALEXANDER, M.D. *Medicine, Psychiatry and their Borderland.* (Shakespeare Head Press Pty. Ltd., Sydney) 21s.
- HALL, I. SIMSON, M.B., CH.B., F.R.C.P.E., F.R.C.S.E. *Diseases of the Nose, Throat and Ear.* Fourth Edition. (E. & S. Livingstone Ltd., Edinburgh) 15s. net.
- JEANS, P. C., A.B., M.D., and MARRIOTT, WILLIAM MCKIM, B.S., M.D. *Infant Nutrition.* Fourth Edition. (Henry Kimpton, London) 32s. 6d. net.
- KINNEAR, JOHN, O.B.E., T.D., M.D., M.R.C.P. (ED.), D.L. *Gardiner's Handbook of Skin Diseases.* Fifth Edition (E. & S. Livingstone Ltd., Edinburgh) 15s. net.
- LLOYD STEVENSON, M.D. *Sir Frederick Banting.* (William Heinemann (Medical Books) Ltd., London) 25s. net.
- MCCORMICK, CHARLES O., A.B., M.D., F.A.C.S. *A Textbook on Pathology of Labor, the Puerperium, and the Newborn.* Second Edition. (Henry Kimpton, London) 42s. net.
- OGILVIE, ROBERTSON F., M.D., F.R.C.P. (EDIN.), F.R.S.E. *Pathological Histology.* Third Edition. (E. & S. Livingstone Ltd., Edinburgh) 37s. 6d. net.
- ROBERTS, R. A., B.SC., M.B., CH.B., D.M.R.E. *Chronic Structural Low Backache due to Low-Back Structural Derangement.* (H. K. Lewis & Co. Ltd., London) 45s. net.
- TODD, A. T., O.B.E., M.B., CH.B., M.R.C.P. *Treatment of Some Chronic and Incurable Diseases.* Second Edition. (John Wright & Sons Ltd., Bristol) 25s. net.
- WALLIS, C. J., M.A. (CANTAB.). *Practical Biology for Medical and Intermediate Students.* Second Edition. (William Heinemann (Medical Books) Ltd., London) 21s. net.

# Edinburgh Medical Journal



# Edinburgh Medical Journal

With which is Incorporated the  
Scottish Medical and Surgical Journal

EDITED BY  
D. MURRAY LYON

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